"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

OWING to our decision to publish six numbers of the *B.J.A.* yearly instead of four it has been necessary to find two new men whose portraits are worthy to stand alongside those of Snow, Simpson, Hickman, and Clover which already adorn the cover of the *B.J.A.* For this purpose we have chosen Buxton and Hewitt. A fuller account of them than we propose to put down here is given in Vol. IV of this Journal in the July and January numbers respectively, to which our readers are referred.

Here we would remind them that Buxton published a book on *Anaesthetics: their uses and administration*, in 1888, which subsequently ran through six editions. He undertook for the *Lancet* the inquiry into the results arrived at by clinical observations. The *Lancet* was never prepared to accept the findings of the Hyderabad Commission and Buxton shared this view. The controversy on how $CHCl_3$ brought about a fatal result did much to arouse interest in anaesthetics. Buxton took a prominent place in these discussions and by his teaching did much to get his students interested in the subject of anaesthesia.

Sir Frederic Hewitt also wrote a book on *Anaesthetics and their administration*, which was perhaps better known and more comprehensive than Buxton's, dealing as it did with the practice of anaesthesia to the exclusion of the history and legal aspect thereof. Hewitt was not only interested in the practice of anaesthesia but also in what we may call the prestige of the subject—the relative importance of it compared with other branches of medicine. He put a high value on this and, in consequence, condemned the state of the law which allowed anybody to give an anaesthetic. It is extraordinary that this state still remains and the public unprotected from the unqualified. It is obvious now that the D.A. and the F.F.A.R.C.S. are the logical outcome of his pioneering efforts. Were he alive today he could not but be grateful for the status that the subject has acquired, and for the number of brilliant men who have been attracted to it, and by whom its prestige has been enhanced still further.

AT the end of January last passed away one of the pioneers of anaesthesia, Hellmuth Weese. Weese was reaching for a book in his library when he fell and suffered a fatal head injury.

He was born in Munich in the year 1897, and was the son of a Professor of History at Berne University. On leaving school he studied medicine at Berne and Zurich, and obtained his medical qualification at Munich. As a result of his researches into the pharmacological investigation of digitalis he was awarded his Doctorate in 1948, and a year later he became Director of the Pharmacological Section at the Wuppertal-Elberfeld

Works of the Bayer Company. His predecessor in this position was Eicholtz, of "Avertin" fame. In 1936 Weese was appointed to the Chair of Pharmacology at the Academie de Medicine in Dusseldorf.

It is true to say that from 1930 onwards Weese devoted his whole time to the study of anaesthetic drugs and substances associated with narcosis and anaesthesia. He investigated the anti-convulsant action of methyl-phenobarbitone (Prominal) and constantly he sought a more controllable substitute for rectal Avertin anaesthesia. When in 1931 Kropp and Taub synthesized for the first time hexobarbitone (Evipan) Weese discovered the remarkably short duration of its action after intravenous injection and realized that here was the possible goal of his quest for controllable anaesthesia. By his introduction into clinical practice of "Evipan" Weese was the forerunner of modern anaesthesia which depends so much on the intravenous administration of narcotic and other drugs. Weese's contribution to the treatment of the patient undergoing surgery did not cease with the introduction of safe intravenous anaesthesia, but he became interested in the search for suitable substitutes for blood. Bayliss had attempted to use gum arabic in 1916, but this was by no means completely satisfactory and it remained for Weese, in collaboration with Hecht, many years later to discover the usefulness in this respect of polyvinylpyrrolidone (Plasmosan).

More modern tendencies in anaesthesia did not escape him, and he was interested in the work of Laborit and Huguenard, which directed his attention to the pharmacology of the phenothiazine derivatives. At his death he was engaged in the investigation of the properties of these drugs with the purpose of rationalizing the empiricism of clinical workers. His death, at a comparatively early age, while still energetically and fruitfully employed in the interests of the specialty and medicine in general, is a severe loss and all anaesthetists would wish to pay tribute to his memory.

To strive to grasp the apparently unattainable, if not the basis of all scientific endeavour, has been the inspiration of many workers. The modern conception of atomic physics has made the alchemist's dream of the transmutation of lead to gold seem not quite so fanciful as it appeared to our fathers. Now pharmacological endeavour is straining to discover drugs with ever more discreet and clear-cut actions. There is, however, an undeniable but very human tendency to hail drugs which appear to exert their pharmacological activity in new directions as panaceas for all ailments. Penicillin suffered to some extent from this tendency, cortisone very much more so, and now chlorpromazine must be added to the list. Certainly anaesthetists are excited by the prospects it seems to offer of controlling the responses of the autonomic nervous system to trauma, responses which may, in certain circumstances, themselves be undesirable and noxious. It cannot be denied also that its effects on personality provide scope for a variation in the premedication of patients for operation under anaesthesia which during the last few years has become almost routine, if not humdrum.

To attempt to read the literature

associated with this drug, although it has only been introduced for about three years would be a task of mammoth dimensions, and quite impracticable for the hard-pressed and fatigued clinician. Dundee, in the current *Educational Supplement*, has attempted to summarize the important literature and to assess to some extent its value in relation to anaesthesia in the widest sense. Complementary to this review Millar's essay on the present position on the much disputed techniques in general anaesthesia associated with this drug will be found helpful by many.

In our more optimistic moments we hope that our readers will peruse all the articles in the *B. J. A.*, and understand at least some of them. But if perchance this is too much to expect we should like to call attention to the article "On Looking up the Literature" kindly written for us by Mr. W. A. Lee, the librarian of the Liverpool Medical Institution, a position which he has held for more than a quarter of a century. If our contributors will take the advice given by this expert it will save not only their own time, but ours.

NEW FILM

The following film has been added to the I.C.I. Film Library:

Relief of Pain in Childbirth. Cat. No. M.33. Running time: 18 minutes. 16 mm. Colour. Made in collaboration with the Department of Gynaecology and Obstetrics, Guy's Hospital, London.

After giving a definition of the ideal obstetric analgesic, a description is given of the two inhalation methods which have become most popular in Great Britain. They employ nitrous oxide and trichlorethylene.

The properties of nitrous oxide are described together with the principles of its administration. The auto-administration by the mother of nitrous oxide and air is the standard method in use. Apparatus for its administration is shown.

"Trilene" is described, together with principles of its administration. Many inhalers are shown. For the successful auto-administration of "Trilene", it is necessary that the inhaler should be capable of delivering the right concentration of trichlorethylene vapour. To do this the inhaler must possess automatic compensating devices for operating under different physical conditions. The latest inhaler, which operates on the principle of a carburettor, is shown.

Finally, the administration of analgesia by either agent is demonstrated and the importance of proper instruction in advance of the time of need is emphasized.

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REBREATHING WITH A SEMI-CLOSED SYSTEM

BY

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THE completeness of carbon dioxide elimination during inhalation anaesthesia is important; and it is generally agreed that it is undesirable to allow the alveolar carbon dioxide to deviate much from normal.

Various methods may be used to estimate the efficiency of carbon dioxide elimination. The alveolar CO_2 tension may be measured. This is an unsatisfactory criterion of the efficiency of the system, because a rise in CO_2 tension may automatically result in an increase in ventilation which will upset the effect being studied.

Instantaneous samples may be taken from near the mouth during one phase of respiration. This will supply information about the concentration involved at the moment of sampling, but not about amounts accumulating or being eliminated in a given time.

A continuous sample of the inspired or of the expired gases may be taken over a relatively long period. This has been done by a number of workers, but has been open to a serious (but often unrecognized) error. The usual method is for gases to be drawn at a steady rate by a pump into a bleeder tube coming off from the breathing circuit close to the facepiece. A pressure operated device starts the pump at the beginning of each inspiratory (or expiratory) phase, and stops it at the end. The pump, while working, withdraws the sample at a steady rate from the gases flowing past the end of the bleeder tube. But these gases do not flow at a steady rate throughout the phase under examination. Their velocity will vary according to the respiratory pattern, and it will be zero at the beginning and end of each respiratory phase. Consequently the pump will withdraw too large a proportion of the gases flowing past the orifice when their velocity is low, and too small a proportion when their velocity is high. The sample will not therefore be a true one.

Molyneux and Pask (1951) have attacked the problem from a physical point of view, and have derived a formula to determine the flow of fresh gases required to avoid any rebreathing for a given ventilation. They did not go into the problem of estimating, for a given ventilation and a given flow of fresh gases, what percentage of CO_2 the inspired air would be expected to contain. This has been the object of the present investigation.

METHOD

In order to permit the variable factors to be altered one at a time, a simple machine was designed to represent the patient. This could give various volumes of tidal air and various respiratory rates, and its CO_2 output—corresponding to the patient's metabolic rate—could be adjusted.

The arrangement is shown diagram-

matically in figure 1. A large respiratory pump (1), of adjustable stroke, is connected to a rubber tube (2), representing the deadspace. Tubes of any desired calibre and length—representing the deadspace of any type of patient—can be used, but in this preliminary investigation the same tube was used throughout. Its bore was 2 cm. and its volume was 150 ml., so that it represented the deadspace of an average adult.

Pure CO_2 is led from a cylinder into a reservoir bag (3), and a tube from this joins the breathing system between the pump representing the lungs and the "deadspace" tube (2) representing the trachea and bronchi. A smaller piston pump (4), also of variable stroke, moves the CO_2 through two one-way valves (5) and a bubbler (6) into the breathing system. The small pump is driven off the same crankshaft (not shown) as the large respiratory pump. It works synchronously with the large pump, but in opposite phase.

The "pharyngeal" end of the tracheal deadspace is connected to the anaesthetic system under study, and a special sampling valve (7) is interposed at this point. This valve consists of a brass cylinder rotating inside an outer sleeve, so that it can assume either of two positions. It is pierced, across its axis of rotation, by three tubes, and the outer sleeve has four connections (*a*, *b*, *c*, and *d*). With the valve in the neutral, or straight-through, position the straight crosstube bridges *a* and *c*, so that the "patient" is connected directly to the anaesthetic machine, and outlets *b* and *d* are blocked. When (as shown in the figure) the valve is put into the sampling position, just before the beginning of an

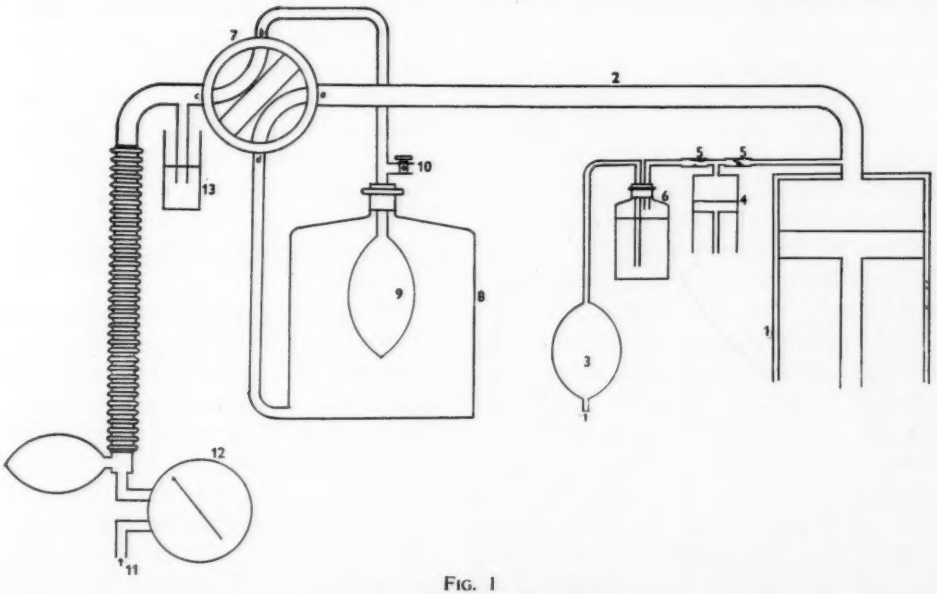

FIG. 1
For description see text.

inspiration, by rotating the inner barrel anti-clockwise one-eighth of a turn, *a* is connected to *d* and *b* to *c*, and the straight crosstube is blocked. On the ensuing inspiration the pump draws its quota not from the anaesthetic machine, but from the bottle (8). This puts a negative pressure on the outside of the rubber bag (9) which is now in direct communication with the breathing system. The gases which would have flowed from the anaesthetic machine to the patient during this inspiration are thus diverted into this sampling reservoir. Moreover this sample consists of the whole of the inspiration and not of a probably unrepresentative portion.

At the end of the inspiration, the valve is clicked back into the straight-through position and the next expiration passes back to the anaesthetic machine. The valve is quick in action, and it is easy to operate it between phases of respiration. In this study, every tenth inspiration was diverted into the sampling reservoir during a run of several minutes. At the end of a run the sample which had been collected in the bag (9) was expelled through the tap (10) by passing gas under pressure into the bottle (8) and submitted to replicate analysis by Haldane's method.

Three arrangements were investigated in this study. One was the common semi-closed system comprising the reservoir bag, corrugated tube and expiratory valve, together known as Magill's attachment (fig. 2). The second was a simple T-piece, with no valves or reservoir bag, as originated by Ayre (1937), in which the fresh gases are led into the pharynx and a wide bore corrugated tube with open end carries away the excess gases and the expired air.

FIG. 2
Magill's attachment.

The third was the arrangement described by Bullough (1952) which combines elements of both the above systems. It consists of a reservoir bag and corrugated tube, into which the fresh gases flow as with Magill's attachment. Instead of the expiratory valve on the facepiece mount, however, a second, open ended, corrugated tube carries the excess flow away from the facepiece.

The anaesthetic machine, to which these arrangements were in turn attached, was reduced to its sole function, for this study, of providing a flow of fresh gases. The vaporizing bottles were omitted, and the gas flow consisted only of oxygen. A bobbin type flowmeter (not shown) indicated approximate flows, and the incoming gas (11, in fig. 1) was led through a paddle type laboratory gas meter (12) which recorded the volume actually delivered during the timed run. The exact flow rate was obtained from this by calculation.

This arrangement enabled various clinical conditions to be simulated. The rate and depth of respiration (though not its form) could be adjusted, and so could the amount of CO_2 liberated into the system per minute. Each quota of CO_2, delivered during the inspiratory phase, was sucked into the chamber of the respiratory pump. This ensured its intimate mixture before its ejection into the system at the next, expiratory, stroke.

RESULTS

For our preliminary investigations, we chose a respiratory rate of 16 and a stroke volume of 400 ml., giving a ventilation of 6.4 l. per minute. With a deadspace of 150 ml. the input of CO_2 per stroke has to be 14.0 ml. to maintain an "alveolar" concentration of 5.6 per cent. Assuming a respiratory quotient of 0.82 and a caloric value for oxygen of 4,825 calories per litre (Best and Taylor, 1945), this corresponds to a metabolic rate of 1,900 calories per 24 hours. This is probably a little more than could be expected clinically.

The Magill's attachment (consisting of a one-litre reservoir bag, 110 cm. (4 ft.) of corrugated rubber tubing of 2.5 cm. internal diameter, and a blow-off valve) was first connected between the source of fresh gas and the "patient". The blow-off valve (13 in fig. 1) consisted of a glass tube with its open end dipping under water. This was substituted for the usual spring loaded type shown in figure 2 because it was more constant in action and because its operating pressure could be accurately adjusted. Two series of runs were made, one with the expiratory valve arranged to blow off at a presure of 1 cm. of H_2O, the other with it set for 5 cm. Various flows of fresh gases, ranging from 10 to 2 l./min., were used.

We found that with 7 l. of fresh gas flowing per min. the concentration of CO_2 attained in the system averaged 0.12 per cent. An increase in flowrate to 10 l. did not reduce this further. We think the small deadspace between the expiratory valve and the sampler, in which CO_2 may be retained, is responsible for this irreducible minimum. This deadspace measured 7 ml., and is thus smaller than that existing under a facepiece.

With smaller flows the concentration of CO_2 increased (see table I) and with a flow of 2 l./min. it reached 3.7 per cent.

TABLE I

Showing the percentage of CO_2 in the inspired air with different flows of fresh gas for the three systems investigated. Tidal air 400 ml. Respiration rate 16 per min. CO_2 input 14 ml. per respiration. Deadspace 150 ml.

Flow per min.	Magill's attachment		Simple T-piece	Bullough's arrangement
	Resistance of blow-off valve			
	1 cm. water	5 cm. water		
10 l.	0.12		1.2	0.56
	0.12		1.4	0.56
	0.12		1.3	0.58
7 l.	0.11	0.11	2.7	0.84
	0.12	0.12	2.7	0.84
	0.15	0.11	2.8	0.90
5 l.	0.22	0.22	4.5	1.3
	0.22	0.22	4.6	1.3
	0.22	0.22	4.8	1.3
3 l.	1.3	1.4	7.6	3.4
	1.4	1.4	7.4	3.8
	1.2	1.5	7.5	3.8
2 l.	3.2	3.7		
	3.1	3.7		
	3.3	3.6		

Changes in resistance of the expiratory valve had no significant effect, the figures for the various flowrates being substantially the same for each series (table I).

The "T-piece" arrangement (fig. 3) was next substituted for the Magill's attachment.

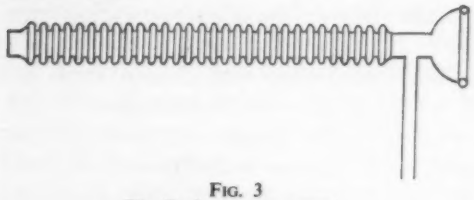

FIG. 3
The T-piece arrangement.

With this system the level of CO_2 attained is considerably higher, reaching 1.3 per cent with a 10 l. flow, and 2.7 per cent with a 7 l. flow (table I).

Bullough's arrangement (fig. 4) was next tried, and gave values which were an improvement on the simple T-piece, but inferior to Magill's attachment (see table I).

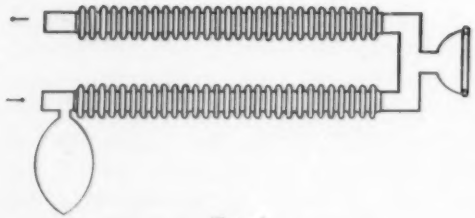

FIG. 4
Bullough's arrangement.

Because we realized that if accumulation of CO_2 occurred in clinical practice the ventilation would be increased while the CO_2 production (metabolic rate) remained at the same level, we did another series of runs in which the stroke volume was increased to 500 ml. and to 700 ml. Flows of fresh gas were limited to 5 l./min. and 7 l./min. (that is to those flows which did permit some accumulation of CO_2). With the Magill's attachment a definite increase in the CO_2 rebreathed resulted: with the T-piece system no such increase occurred; and with Bullough's arrangement the increase was small (see table II).

The CO_2 concentration with each of the three systems is compared in figure 5.

DISCUSSION

Magill's attachment is a simple and effective means of eliminating CO_2 in semi-closed anaesthesia. A very large flow of fresh gas is needed to ensure that *no* part of the patient's expiration is returned to the system, but because the deadspace air (which is the part that is

TABLE II

Showing the percentage of CO_2 in the inspired air, for the three systems investigated, when the tidal air was increased. Other parameters as in table I.

Circuit	Magill's attachment			Simple T-piece			Bullough's arrangement		
Tidal air	400	500	700	400	500	700	400	500	700
Flow per min.									
	0.11	0.15	0.45	2.7	2.7	2.7	0.84	0.87	0.99
7 l.	0.12	0.17	0.64	2.8	2.8	2.8	0.84	0.80	0.99
	0.15	0.16	0.54	2.8			0.90		
	0.22	0.44	1.4	4.5	4.3	4.0	1.3	1.4	1.8
5 l.	0.22	0.45	1.4	4.6	4.3	4.0	1.3	1.4	1.8
	0.22	0.44	1.6	4.8			1.3		

likely to be rebreathed) contains little CO_2, a flow of 7 l./min. seems to limit the accumulation of CO_2 to a satisfactory level. This corresponds well enough with the figure derived from Molyneux and Pask's (1951) formula, according to which rebreathing of any alveolar air would be prevented, at this level of ventilation, by a flow of fresh gas of 5.8 l./min. The corresponding point on our curve (fig. 5) would give a CO_2 level of between 0.1 and 0.2 per cent. This also conforms to clinical experience; for with a flow of 7 l./min. and a Magill's attachment, troublesome CO_2 accumulation is rare. If this should occur, however, and the patient responds by increasing his tidal air, this will make matters worse, as Molyneux and Pask have pointed out, and a vicious circle may be started. This is merely an expression of the fact that increased ventilation needs increased flow rate to prevent rebreathing.

The valveless T-piece system favoured in some form by many anaesthetists seems to be much inferior to Magill's attachment for getting rid of CO_2. A brief consideration of the two systems explains this. With Magill's attachment the first part of the expiration—the deadspace air, which contains little CO_2—remains in the system and is rebreathed, and the last part, which

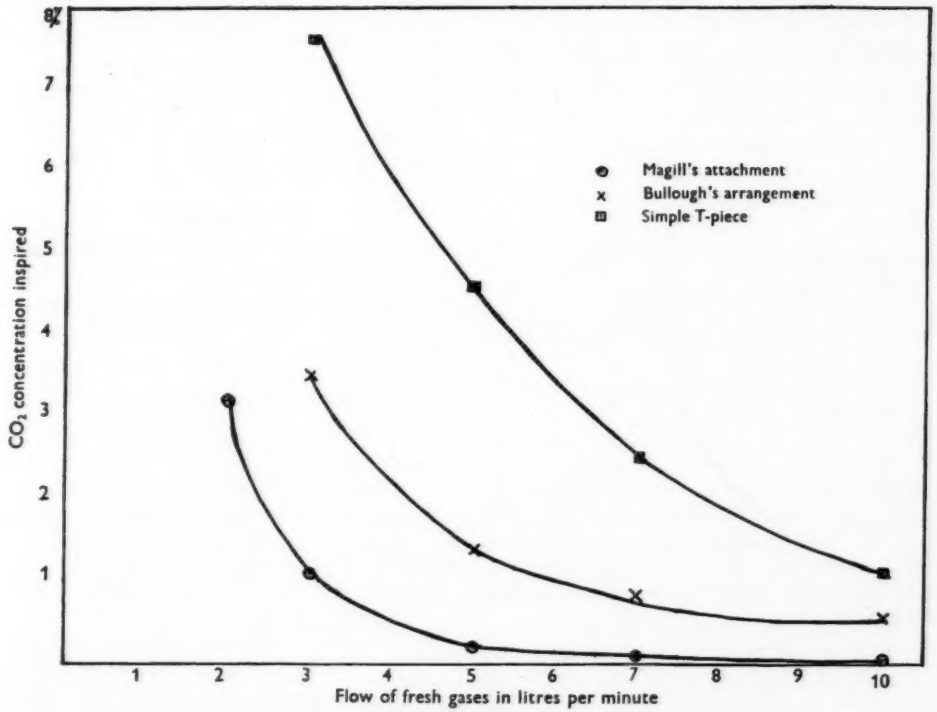

FIG. 5

CO_2 concentration in the inspired air with various flows of fresh gases for each of the three systems.

is alveolar air, escapes from the expiratory valve when it opens. With the T-piece system, it is the deadspace air which escapes from the open end of the tube, and it is the last portion of expiration, which is rich in CO_2, that remains in the tube to be inspired at the next breath.

On the other hand, with the T-piece system no increase in CO_2 accumulation was found to be caused by increasing the tidal air. The reason for this is as follows. The volume of the corrugated tube was 550 ml. This is enough to prevent outside air from entering the "patient" when the tidal air is 400 ml. When the tidal air increases enough to exceed the volume of the corrugated tube, outside air will be inhaled to dilute the CO_2. Relatively considered, the deadspace is reduced. The dilution by outside air which is possible with this arrangement may also cause anaesthesia to become too light.

ACCURACY AND SOURCES OF ERROR

CO_2 was measured by Haldane's apparatus. Replicate analyses were in good agreement.

The flow of fresh gas was measured during each run by a Parkinson and Cowan gas meter, and the runs were timed by a stopwatch. Variations did not exceed 1 per cent.

The speed of the pump was constant to within ± 2.5 per cent.

The sampling valve was not worked automatically, but was snapped from one position to the other by hand. This was not difficult, but the small variations in concentration observed from run to run with the same setting may be due to errors in operation. Our samples of inspired air were found to be about 80 per cent of the ideal volume.

An arrangement such as that described, with a "mechanical patient", makes it easy to control variable factors in a way which would be impossible with a living subject, and provides a useful means of studying the physical factors involved.

CONCLUSIONS

(1) For the average adult patient with normal metabolic rate and corresponding ventilation, a flow of fresh gas of 7 l./min. into a Magill's attachment will limit the percentage of CO_2 rebreathed to a satisfactory level.

(2) The tension of the expiratory valve does not influence the elimination of CO_2.

(3) Magill's attachment is superior to the simple T-piece system for eliminating CO_2.

(4) The modification of Magill's attachment described by Bullough, by which an open ended tube is substituted for the expiratory valve, decreases its efficiency in the elimination of CO_2.

ACKNOWLEDGMENT

It is a pleasure to acknowledge our indebtedness to Dr. E. Lundsgaard, Professor of Physiology in the University of Copenhagen, in whose Department this work was begun and who gave us valuable help and advice.

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Brit. J. Anaesth. (1954), **26**, 323.

THE ELIMINATION OF REBREATHING IN VARIOUS SEMI-CLOSED ANAESTHETIC SYSTEMS

BY

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INTRODUCTION

A VALUABLE theoretical and experimental analysis of the flow of gases in a semi-closed anaesthetic system was published by Molyneux and Pask in 1951. Their theoretical analysis was applied to one particular type of system and involved the assumption of certain idealized characteristics of the expiratory valve and of the breathing pattern. In the present work it is proposed to extend the theoretical analysis to other types of semi-closed systems and to take account of the effects of the actual characteristics of the expiratory valve and reservoir bag and of breathing patterns other than the idealized one.

In all, five systems will be considered (A, B, C, D, E in figure 1) of which A was analyzed by Molyneux and Pask.

SYSTEM A

Expiratory valve close to face mask, separated by corrugated tube from reservoir bag and supply of fresh gases.

In this simple analysis the following assumptions will be made:

(1) Gas enters the system from the anaesthetic machine at a constant volume flowrate F_a.

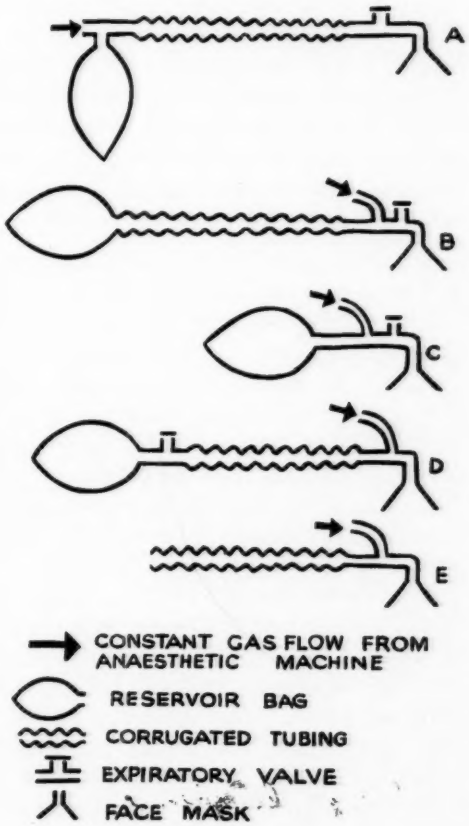

FIG. 1

The five semi-closed anaesthetic systems.

(2) At the start of inspiration the flow-rate into the lungs rises instantaneously to some value greater than F_a. No other assumption need be made as to the nature of the breathing pattern.

(3) The expiratory valve opens when the pressure in the system exceeds some critical value slightly above atmospheric and the valve will pass large flows without further increase in the pressure drop across it.

(4) The system is in a stable state—that is to say the conditions at any particular moment in the cycle of respiration are constant from one respiration to another.

(5) "Plug" flow occurs in the corrugated tubing, face mask and patient's trachea—that is, no longitudinal mixing occurs in these regions.

During expiration gases will enter the system at a known constant rate, F_a, from the anaesthetic machine and an unknown varying rate, say f_r, from the patient. Initially the fresh anaesthetic gases will flow directly into the bag while the expired gases will flow back along the corrugated tubing, forcing gas from the tubing into the bag. When the bag volume rises to some critical value, say V_o, at which the pressure inside it is equal to the opening pressure of the expiratory valve, the valve will open. Then, in virtue of assumption 3, the pressure in the system will not rise further and the volume of the bag will remain constant at V_o. The expired gases will flow directly out through the valve at an unknown varying rate which may still be represented by f_r, while the fresh anaesthetic gases will flow forward along the corrugated tubing still at the known constant rate F_a, forcing out through the expiratory valve gas which had previously entered the corrugated tube from the patient at the beginning of expiration. Apart from the variation of f_r conditions will then remain constant until the start of inspiration.

At the start of inspiration, in virtue of assumption 2, gas will be drawn from the system by the patient faster than it enters from the anaesthetic machine. The additional gas must necessarily be drawn from the reservoir bag whose volume will therefore decrease. Immediately this volume reduction starts there will be a corresponding reduction in the pressure in the system (Mapleson, 1954) below the opening pressure of the expiratory valve which will consequently close immediately inspiration begins. Thereafter conditions will remain steady, the bag slowly emptying, until the rate of inspiration, f_r, falls below the rate of supply of fresh gases, F_a, when the bag will begin to refill. When expiration commences the bag will fill comparatively rapidly in the manner described at the beginning of this analysis. Now let V_t = patient's tidal volume.

T_1 = time from the start of one inspiration to the end of the same inspiration.

T_2 = time from the end of one inspiration to the start of the next inspiration.

T = duration of one complete respiratory cycle = $T_1 + T_2$.

T' = time from the end of inspiration to the opening of the expiratory valve.

Then the volume drawn from the bag during inspiration will be $V_t - F_a T_1$.

This volume is replaced during expiration in a time, T'. A portion, $F_a T'$, will come direct from the anaesthetic machine, while the remainder, $V_t - F_a T_1 - F_a T'$, will come from the patient. This last volume, $V_t - F_a T_1 - F_a T'$, is thus the volume of expired gas which enters the corrugated tubing and, at the instant at which the valve opens, will reside in the right-hand end of the tube (fig. 1, A), assuming, as one reasonably may in all normal circumstances, that this volume is less than the volume of the corrugated tubing. During the remainder of the time $T_2 - T'$ before the next inspiration, a volume, $F_a T_2 - F_a T'$, of fresh anaesthetic gas will enter the corrugated tubing from the machine at the left (fig. 1, A) and drive out through the expiratory valve at the right an equal volume of the expired gases residing in the right-hand end of the tubing. At the start of the next inspiration, therefore, the volume of expired gas still remaining in the corrugated tubing will be $V_t - F_a T_1 - F_a T' - F_a T_2 + F_a T' = V_t - F_a T$. However, this volume will be composed of gas which was breathed out at the beginning of expiration. Therefore, provided this volume does not exceed V_s, the dead space of the patient plus mask, it will not contain any gas which has been in contact with the alveoli of the lungs—that is to say, it will not contain any "contaminated" gas. Thus a criterion for the elimination of rebreathing may be expressed mathematically by:

$$V_t - F_a T \leqslant V_s$$

or

$$F_a \geqslant (V_t - V_s)/T \quad \ldots\ldots\ldots\ldots (1)$$

Now V_t/T is one tidal volume divided by the period of one respiratory cycle and consequently is equal to the minute volume.* Similarly, $(V_t - V_s)/T$ may be referred to as the "effective" minute volume, since it is equal to the average rate of supply of fresh gases to the alveoli of the lungs. Then the criterion for the elimination of rebreathing may be expressed in words by:

> "The volume flowrate of anaesthetic mixture must be not less than the patient's effective minute volume."

It will be realized that this criterion is considerably at variance with that established by Molyneux and Pask. This is due, of course, to the different assumptions made in the present analysis. It is now proposed to examine the effect of various inaccuracies involved in some of these assumptions.

Assumption 5 clearly represents a highly idealized state of affairs; some longitudinal mixing is bound to occur in the system so that when equation (1) is just satisfied some "contaminated" expired gas will, in fact, still reside in the corrugated tubing at the beginning of inspiration and will consequently be rebreathed. In order to *ensure* the elimination of rebreathing, therefore, the criterion:

$$F_a \geqslant V_t/T \quad \ldots\ldots\ldots\ldots (2)$$

might be adopted. That is to say that the flow of fresh gas must be not less than the patient's actual minute volume. It imposes the condition that in the absence of mixing none of the gas from the previous expiration shall remain in the system at the start of inspiration. Since mixing will occur some small volume of expired gas will in

* Minute volume (F_m) = tidal volume (V_t) × number of respiratory cycles per minute (n). Now, $n = 1/T$ (T in minutes); therefore, $F_m = V_t/T$.

fact remain (an equal volume of fresh gas having escaped through the expiratory valve to maintain the balance) but it will probably consist mainly of gas which has not been in contact with the alveoli of the lungs. Molyneux and Pask took an even stricter condition: namely, that the volume of expired gas which *initially* flows back into the corrugated tube shall not exceed the total deadspace. That is to say

$$V_t - F_a(T_1 + T') \leqslant V_s$$

or $$F_a \geqslant (V_t - V_s) / (T_1 + T') \ldots\ldots(3)$$

Even with this condition, however, it is still just possible that mixing would lead to some small amount of rebreathing. In the limit, therefore, it could be assumed that rebreathing will be completely eliminated only if no expired gas is allowed to enter the corrugated tube at any time. That is to say $V_t - F_a(T_1 + T') \leqslant O$ or, since in this condition T' must equal O

$$F_a \geqslant V_t/T \ldots\ldots\ldots\ldots(4)$$

(If the periods of inspiration and expiration are equal this is equivalent to saying that the flow of fresh gases must be at least equal to twice the actual minute volume.) If no mixing occurred a graph of percentage rebreathing against the ratio F_a/F_m where F_m is the actual minute volume would appear somewhat as the solid line of figure 2. With mixing, the graph would be modified to something like that shown by the dotted line in the same figure. It would appear that the only way to determine the exact nature of the dotted line would be to perform rapid continuous gas analysis within the semi-closed system. Until this is done and until an acceptable minimum percentage of rebreathing is agreed, it seems that the choice of the condition to establish a criterion for the effective elimination of rebreathing is largely arbitrary. In the author's opinion, quite a small increase in the flow of fresh gases above the minimum required by equation (1) would probably be sufficient to reduce the amount of rebreathing to an acceptably low level.

Instead of making assumption 2, let account be taken of the measurements of Proctor and Hardy (1949), which show that with a patient inspiring against negligible resistance (which will be the case in these semi-closed systems) the inspiratory flowrate increases gradually (though rapidly), and not instantaneously, at the beginning of inspiration. Thus there will be some short period of duration, say T_3, at the beginning of inspiration during which the inspiratory flowrate will be less than the flow of fresh gas from the machine. During this period, therefore,

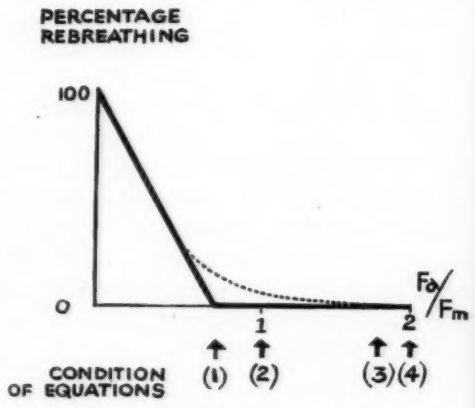

FIG. 2

Graph of percentage rebreathing against the ratio F_a/F_m (flowrate of fresh gases over patient's minute volume) for system A. Solid line: theoretical curve in the absence of longitudinal mixing. Broken line: assumed curve in the presence of mixing.

some of the gas in the right-hand end of the tube will enter the patient and some will leave through the expiratory valve. This state of affairs will persist until the inspiratory flowrate exceeds F_a when the valve will shut and the bag volume begin to decrease.

During this period a volume of gas, $F_a\ T_3$, will flow from the anaesthetic machine. If the rate of increase of inspiratory flow is constant during this period, half of this volume, namely $F_a\ T_3/2$, will enter the patient, and half will leave through the expiratory valve. Now during the remainder of the inspiration the patient will draw the remainder of the tidal volume, $V_t - F_a\ T_3/2$, and the anaesthetic machine will supply a volume, $F_a\ (T_1 - T_3)$ of fresh gas. The difference, $V_t - F_a\ T_1 + F_a\ T_3/2$, will be drawn from the bag. At a time T' after the end of inspiration, the bag will have regained its critical volume V_o, F_aT' coming from the anaesthetic machine and the remainder, $V_t - F_a\ (T_1 - T_3/2 + T')$, coming from the patient's expiration (into the right-hand end of the corrugated tube). During the rest of the time up to the start of inspiration $(T_2 - T')$ a volume, $F_a\ (T_2 - T')$, of fresh gas will enter the left-hand end of the tube, driving out through the expiratory valve all but $V_t - F_a\ (T_1 - T_3/2 + T') - F_a\ (T_2 - T') = V_t - F_a\ (T - T_3/2)$ of the patient's expiration. Then, assuming that no longitudinal mixing occurs, it is this volume which must contain no "contaminated" expired gas if rebreathing is to be eliminated.

That is $V_t - F_a\ (T - T_3/2) \leqslant V_s$

or $F_a \geqslant (V_t - V_s)/(T - T_3/2)$.....(5)

From the graphs given by Proctor and Hardy it is apparent that, when F_a is about equal either to the effective or to the actual minute volume of the patient, T_3 is only about a tenth of T so that equation (5) differs only by a twentieth or a factor 1.05 from equation (1) and it is apparent that assumption 2 introduces no appreciable error.

Now let assumption 3 be modified to take account of the increase in pressure drop across the valve which occurs with an increase of flow through the valve (Mushin and Mapleson, 1954). Let the expiratory valve close at a time, T_4, after the start of inspiration and during this period let the patient inspire a volume, V_p. When the valve closes the bag volume will be V_o and therefore at the end of inspiration it will be say, $V_1 = V_o - \{V_t - V_p - F_a\ (T_1 - T_4)\}$. Let the bag volume at the beginning of inspiration be V_2. Then the net flow of expired gas into the corrugated tube will be $V_2 - V_1 - F_a\ T_2 = V - V_o + V_t - V_p - F_a\ (T - T_4)$. This must be not greater than V_s for the elimination of rebreathing, in the absence of mixing. Therefore

$$F_a \geqslant \frac{V_t - V_s + (V_2 - V_o - V_p)}{T - T_4} \quad \ldots\ldots(6)$$

In order to allot numerical values to the quantities $(V_2 - V_o - V_p)$ and T_4 it is necessary to assume some definite shape for the respiratory flowrate curve and to apply a somewhat lengthy mathematical analysis which it is felt would be somewhat out of place here. However, it can be shown that under all conditions of respiration and valve and bag characteristics likely to be encountered in clinical practice the minimum value required for F_a in order to eliminate rebreathing while

being, of course, greater than $(V_t - V_s)/T$ (the effective minute volume) will not be so great as V_t/T (the actual minute volume).

Assumptions 1 and 4 merely restrict the applicability of the analysis to steady conditions.

Thus it seems probable that the errors introduced by assumptions 2, 3 and 5 could be allowed for by adopting equation 2 rather than equation 1. That is to say that it is probably safe to assume that in system A rebreathing of gas which has been in contact with the alveoli of the lungs will be almost completely prevented if the flow of fresh anaesthetic gas is at least equal to the patient's minute volume.

SYSTEM B

Expiratory valve and supply of fresh gases close to face mask, separated by corrugated tube from reservoir bag.

The same assumptions will be made here as for system A. Some time during expiration the bag will fill to the critical volume V_o, and the expiratory valve will open, fresh gas passing directly out at a rate F_a and expired gas at f_r. At the start of inspiration the valve will close and gas will enter the patient at a rate F_a from the machine and a rate $f_r - F_a$ from the corrugated tubing and bag until the full tidal volume V_t has been drawn. Then, at the start of expiration, fresh gas will flow at a rate F_a and expired gas at a rate f_r back along the corrugated tube until the bag volume again reaches V_o and the valve again opens.

Now the volume drawn from the corrugated tube and bag during inspiration $= V_t - F_aT_1$. Of this, $F_a T'$ will be replaced by fresh gas and the remainder, $V_t - F_aT_1 - F_aT'$, by expired gas. This gas will remain in the corrugated tube until inspiration begins since, when the expiratory valve is open, the fresh gases will leave directly through it instead of displacing expired gas from the tube as in system A.

Thus the amount of gas which will be rebreathed is $V_t - F_a T_1 - F_a T'$. Since this rebreathed gas entered the corrugated tubing at the start of expiration, it may be assumed that the rebreathing of contaminated gas will be eliminated if

$$V_t - F_a T_1 - F_a T' \leqslant V_s$$

that is, if $F_a \geqslant (V_t - V_s)/(T_1 + T')$...(7)

Now unless some assumption is made as to the form of the expiratory flowrate curve, T' is indeterminate. However, it must be less than T_2 and therefore $T_1 + T'$ must be less than T. Thus to eliminate rebreathing the flow of gases from the anaesthetic machine must exceed some value which itself is appreciably greater than the patient's effective minute volume. Thus a higher flowrate is needed in this system than in system A.

As in system A, equation (7) holds good only on the assumption (No. 5) that no mixing occurs in the patient's trachea and the face mask. If mixing is assumed to occur there, then the volume of expired gas which is permitted to enter the corrugated tube must be more severely restricted and in the limit *no* expired gas can be permitted to enter it. That is to say, $V_t - F_a T_1 - F_a T' \leqslant O$. Since T' must now equal O,

$$F_a \geqslant V_t/T_1 \text{ .....(8)}$$

Remembering that V_t/T is the patient's minute volume and that the measurements of Proctor and Hardy (1949) have shown

that the duration of inspiration (T_1) is usually rather less than half the respiratory period (T) it is evident that the flow of fresh gas must be at least rather more than twice the minute volume of the patient.

If assumption 2 is modified to take account of the fact that the expiratory valve will not close until some finite time, T_3, after the start of inspiration, then it can be shown that equation (7) is modified to

$$F_a \geqslant (V_t - V_s)/(T_1 + T' - T_3/2) \ldots . (9)$$

As in system A, however, this represents only a very small change in the criterion, since T_3 will be only about one-tenth of T.

It is more difficult to determine what will happen if assumption 3 is modified to take account of the increase in pressure drop across the valve which accompanies an increase in flow through it. After the valve has just opened the pressure in the system will increase as the flow through the valve increases and consequently the volume of the bag will increase. If the pressure-flowrate characteristic of the valve has a gentle slope (that is, large flows can be passed for small increases of pressure above the opening pressure) only a small extra volume, including some expired gas, will enter the bag. Depending on the nature of the breathing pattern, some of this volume may still reside in the corrugated tube at the start of inspiration and so be rebreathed. If, however, the characteristic has a steep slope an appreciable volume would enter the bag, and to prevent this containing any "contaminated" expired gas it would be necessary to ensure that the bag reached its maximum volume early in expiration, before the expiration contained any gas which had been in contact with the alveoli of the lungs. It can be shown that this can be achieved if the valve first opens very soon after the start of expiration—in other words, if the fresh gas supplied by the machine during inspiration is almost as large as the patient's tidal volume.

Thus when account is taken of the effect of the various errors introduced by assumptions 2, 3 and 5 it seems probable that rebreathing of contaminated gas will be almost, if not quite, eliminated provided that the supply of fresh gas is at least equal to twice the patient's minute volume.

SYSTEM C

Expiratory valve, supply of fresh gases and reservoir bag, all close to face mask. (No corrugated tube.)

From figure 1 it is apparent that system C can be regarded as a limiting case of either system A or B in which the length of the corrugated tubing has been reduced to zero. The flow conditions of system A will be seriously altered when the length of the corrugated tube approaches zero since it can then no longer act as a depot in which the early part of expiration can temporarily reside, to be driven out of the expiratory valve, later in the expiratory phase, by fresh gases. In system B, however, the tubing merely forms an extension of the reservoir bag so that the conditions for the elimination of rebreathing in system C are the same as those in system B. If, however, any rebreathing does occur, the way in which the concentration of carbon dioxide builds up in the inspired air may well be different since mixing of each expiration with the gas in the bag will occur more efficiently in this system than in system B.

SYSTEM D

Supply of fresh gases close to face mask, separated by corrugated tube from reservoir bag and expiratory valve.

In this system during expiration fresh gas and expired gas will flow together, backwards along the corrugated tube, initially into the bag and later, when the bag has attained its critical volume, V_a, out through the expiratory valve. During inspiration, fresh gas will flow directly to the patient at a rate F_a, the remainder of the patient's inspiratory requirements being drawn along the corrugated tube from the bag.

The conditions in this system are clearly rather different from those in the three systems already considered. Any expired gas which enters the corrugated tube and is subsequently inspired will undoubtedly have been in contact with the alveoli of the lungs since it was derived from the last part of expiration. Thus, for the complete elimination of rebreathing, *no* gas from the previous expiration must be allowed to enter the lungs. The only condition under which gas may be drawn from the corrugated tubing during inspiration is if between the end of expiration and the beginning of inspiration there is a pause of duration, say T'', during which a volume of fresh gas, $F_a\,T''$, will accumulate in the right-hand end of the corrugated tube.

Then this volume, plus that supplied by the anaesthetic machine, must be not less than the tidal volume.

That is $F_a\,T'' + F_a\,T_1 \geqslant V_t$

or $F_a \geqslant V_t/(T_1 + T'')$ .....(10)

Since T'' is rarely more than a small fraction of T, the period of the respiratory cycle, this condition is approximately the same as that given by equation (8). Here it will hold true whatever the nature of the expiratory flowrate pattern (since T'' may be put equal to O if necessary), but it may be rendered false by certain types of inspiratory flowrate patterns. If $T'' = O$ then no gas must be drawn from the corrugated tube during inspiration. If the inspiratory flowrate pattern is a perfect square wave, then the assumption made above ($F_a\,T_1 \geqslant V_t$ when $T'' = O$) is justified, since the inspiratory flowrate will be constant and not greater than F_a during inspiration. However, if for the same tidal volume the inspiratory flowrate pattern is at all "peaky" some small volume of gas will at some stage during inspiration be drawn from the corrugated tube to be replaced by an equal volume of fresh gas from the anaesthetic machine towards the end of inspiration. If there is an appreciable expiratory pause ($T'' \neq O$) there would probably be a sufficient volume of fresh gas in the right-hand end of the corrugated tube to act as a buffer against this effect.

In this system there is no need to make assumptions 2, 3 and 5. It can be stated that rebreathing will be eliminated, providing the inspiratory flowrate pattern is not too "peaky", if the supply of fresh gas is at least equal to some value slightly greater than twice the patient's minute volume.

SYSTEM E

Supply of fresh gases close to face mask. Open length of corrugated tube. No reservoir bag or expiratory valve.

The conditions in this system are little different from those in system D except that during inspiration some fresh air may

be drawn into the left-hand end of the tube and during expiration both expired gases and fresh gas from the machine will pass backwards along the corrugated tube straight out into the air. Assuming that wide bore connectors and tubing are used, the resistance of the system is very low. Therefore, the inspiratory flowrate pattern will be appreciably "peaky", but there will be an appreciable expiratory pause (Proctor and Hardy, 1949) so that the conditions for the elimination of rebreathing will be approximately the same as in system D.

Another method of eliminating rebreathing in this system is to use a very short length of corrugated tube. Suppose there is a definite pause, of duration T'', between the end of expiration and the start of inspiration. Then a volume, F_aT'', of fresh anaesthetic gases will enter the corrugated tube during this time. If the volume of the tube is no greater than this, then no rebreathing can occur (assuming that the expired gases are swept away from the end of the tube by draughts). However, if advantage is taken of this fact, the anaesthetic mixture will be diluted by fresh air unless $F_a(T_i + T'')$ is at least equal to V_t. That is to say, that the flow of fresh gases must be at least equal to about twice the patient's minute volume.

Thus, if there is an expiratory pause, rebreathing can be eliminated in this system by using a length of corrugated tubing whose volume is no greater than the product of the duration of the expiratory pause and the flowrate of fresh anaesthetic gases, but the anaesthetic mixture will then generally be diluted by fresh air. If it is desired to avoid this dilution as well as eliminate rebreathing, then the flowrate of fresh gases must be at least equal to twice the patient's minute volume and then the length of the corrugated tubing is of little consequence except from the point of view of resistance.

CONCLUSIONS

From these results it is apparent that system A has a marked advantage over the others from the point of view of economy of gases (assuming that it is desired to eliminate rebreathing). On the other hand, system E has a marked advantage over the others from the point of view of resistance to breathing—all the other systems involve the use of an expiratory valve which imposes an appreciable resistance to expiration, particularly when it is passing a large flow (Mapleson and Mushin, 1954) as it will be with the high flowrates of anaesthetic gases required to eliminate rebreathing in systems B, C, and D.

SUMMARY

The flow of gases in five different semi-closed anaesthetic systems is examined theoretically. The minimum flowrate of fresh anaesthetic gases required to eliminate rebreathing is determined in each case.

The results may be summarized by saying that rebreathing has probably been eliminated if the flow of fresh gases is at least equal to the patient's minute volume in system A (fig. 1) and at least equal to about twice the minute volume in systems B, C, D, and E. Rebreathing can also be eliminated in system E with a smaller flow of gas if there is an expiratory pause and if the volume of the corrugated tube is no greater than the product of the duration of this pause and the flowrate of fresh

anaesthetic gases, but then the anaesthetic mixture will generally be diluted with fresh air.

ACKNOWLEDGMENTS

The author's thanks are due to Professor William W. Mushin for encouragement and to Miss June Williams for the figures.

LIST OF SYMBOLS USED

f_r = volume flowrate of gases to or from the patient.
F_a = volume flowrate of fresh gases from the anaesthetic machine.
F_m = patient's minute volume.
n = number of respiratory cycles per minute.
T = duration of one complete respiratory cycle = $T_1 + T_2$.
T_1 = time from the start of one inspiration to the end of the same inspiration.
T_2 = time from the end of one inspiration to the start of the next inspiration.
T_3 = duration of the period at the beginning of inspiration in which $f_r < F_a$.
T_4 = time from the start of inspiration to closure of the expiratory valve (when taking account of the real valve characteristic).
T' = time from the end of inspiration to the opening of the expiratory valve.
T'' = time from the end of one expiration to the start of the next inspiration (" expiratory pause ").
V_o = volume of reservoir bag when the pressure inside it is equal to the opening pressure of the expiratory valve.
V_1 = volume of reservoir bag at the end of inspiration.
V_2 = volume of reservoir bag at the beginning of inspiration (when taking account of the real valve characteristic).
V_p = volume inspired by the patient during the period T_4.
V_d = deadspace of patient plus face mask.
V_t = patient's tidal volume.

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SOME DATA ON THE PERFORMANCE OF WATERS CANISTER

BY

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IT has been known, since the introduction of soda lime as a carbon dioxide absorbent for clinical use in anaesthetics, that the canister must be packed firmly with the granules to achieve efficient absorption. It has been assumed that if the canister was filled to capacity, with the contents shaken down, it would perform satisfactorily. Our clinical experience, however, has shown that one could not expect five hours of efficient absorption from one charge of soda lime in a Waters canister. Various brands of soda lime were therefore tested in the laboratory in order to select the most efficient variety for hospital use. Some features of the performance of Waters canister have become apparent during these tests which we feel ought to be more widely known.

The soda lime was tested as follows: "To and fro" ventilation of a Waters canister and bag was carried out with a respiratory pump, arranged to give a tidal volume of 500 ml., 12 times per minute, inspiration and expiration being equal and with an end expiratory pause. A carefully metered constant flow of carbon dioxide of 200 ml./minute was admitted to the "patient's" side of the system, and a sample of the "bag" gases was fed to an infra-red analyser with each inspiration. The sampled gas was fed back into the "patient" to maintain the operating volume of the system.

Figure 1 (lines 1, 2 and 3) shows the results obtained with three samples of one brand of soda lime. The canister was packed in the normal manner and laid horizontally during the test. These rather disturbing results led us to estimate the carbon dioxide in the bag of Waters assembly in clinical use, and we found carbon dioxide concentrations higher than we consider desirable (table I).

TABLE I

Performance of fresh charge in Waters canister, normal packing

Time from start Minutes	Bag CO_2 per cent			
	Case 1	Case 2	Case 3	Case 4
5	1.0	0.9	—	0.5
10	1.2	1.35	—	0.53
15	1.4	0.85	0.45	1.0
20	2.0	1.65	0.4	0.35
25	—	0.9	0.975	0.35
30	—	0.7	0.95	0.65
35	—	1.05	0.55	0.55
40	—	—	0.425	0.35
45	—	—	—	0.95
50	—	—	—	0.55
55	—	—	—	0.45
60	—	—	—	0.55

It was found that if the canister was placed vertically and shaken to settle the granules, the performance improved remarkably, the results being shown in figure 1 (lines 4 and 5).

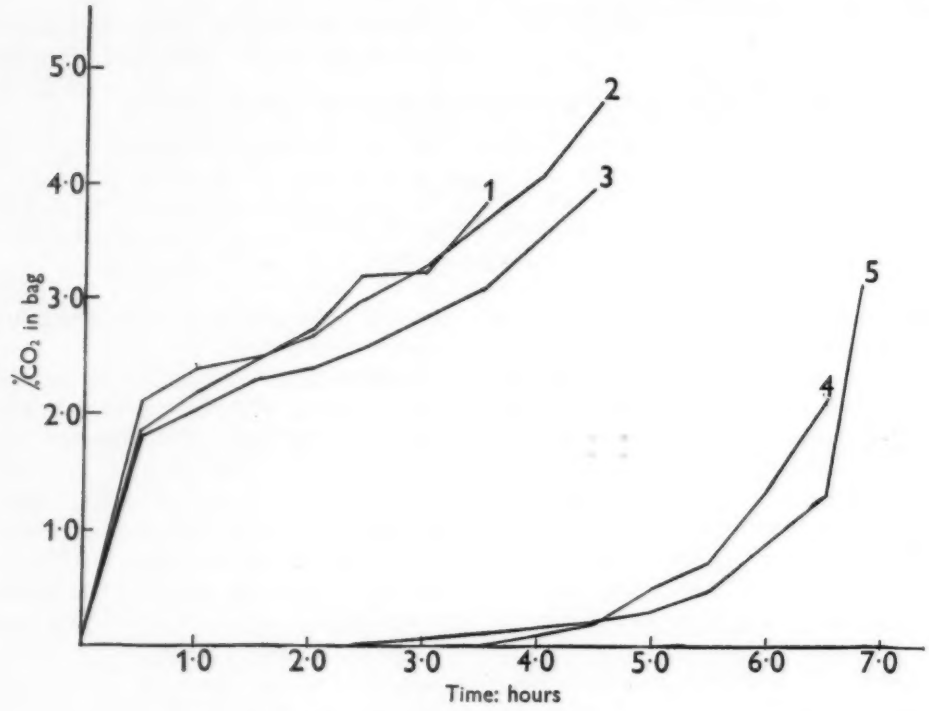

FIG. 1

Lines 1, 2 and 3 show the rise of carbon dioxide concentration using the experimental test arrangement with a Waters canister packed in the conventional manner and laid horizontally. Lines 4 and 5 show the rise of carbon dioxide when a conventionally packed canister is held in the vertical position.

If such a canister during test was laid flat with care, it would continue to absorb efficiently, but if it was disturbed by tapping the bag, carbon dioxide would at once rise. It was obvious that in canisters so packed, channelling occurred very easily and that some more efficient means of packing with soda lime was required. In table I, the variations in concentration of carbon dioxide can be accounted for by the periodical disturbance of the canister. After various trials it was found that the correct degree of elastic compression of the charge could be obtained with a simple nylon pot scrub. This offers minimal resistance to air flow, the material seems unaffected by alkali and moisture, and may be autoclaved. The canister is filled and shaken down as tightly as possible, and the nylon scrub inserted so as to leave about half of it to be compressed by the wire gauze in the lid of the canister when the cap is screwed on (figs. 3 and 4).

Canisters packed in this fashion gave results as in figure 2. Movement of the

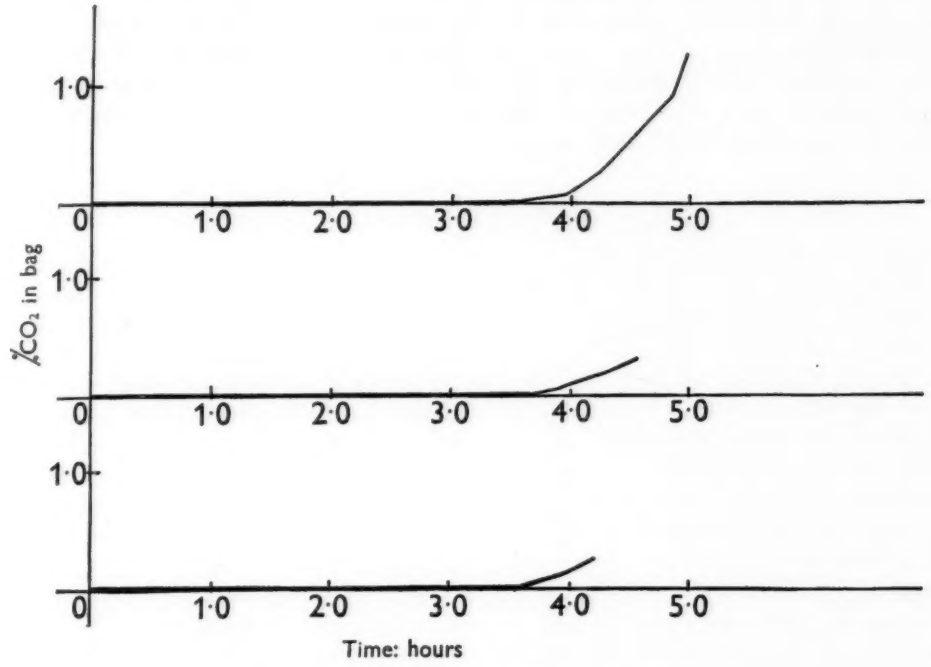

FIG. 2
Rise of carbon dioxide concentration using Waters canisters packed by the suggested method, the canister being horizontal.

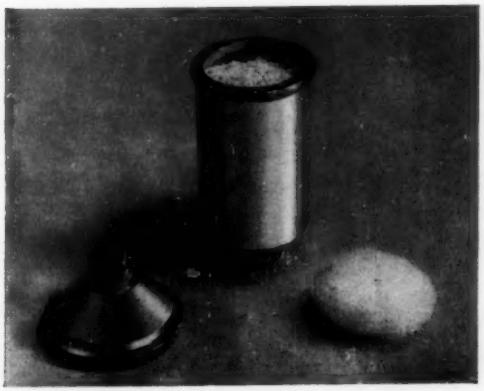

FIG. 3

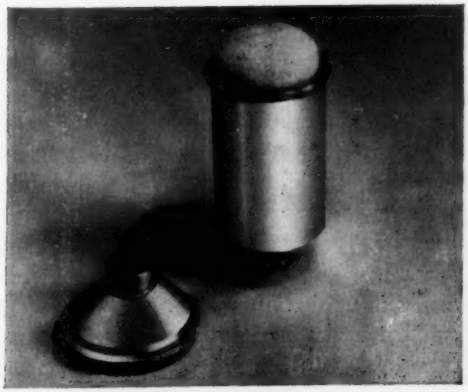

FIG. 4

canister in no way affected the efficiency. These results have been confirmed in clinical practice.

The resistance of a conventionally packed canister at a flow rate of 40 l./min. was found to be 4.2 mm. water. With the canister packed as described the resistance was 7.8 mm. water. The slight increase in resistance is probably due to the fact that the respiratory gases must now pass through, rather than round, the soda lime.

BOOK REVIEW

A Synopsis of Anaesthesia. By J. A. Lee. Published by John Wright & Sons, Ltd. Pp. 457; 72 illustrations. Price 21*s*.

It is a pleasure to welcome the third edition of this excellent work, which appears three years after the second edition and seven years after the first.

Inevitably it is larger, and more expensive, than the last edition. Its size has increased by 36 per cent and its price by 40 per cent. It is still, nevertheless, a masterpiece of compression, and it is probable that more useful information is contained per page than in any other book on anaesthesia.

Two new chapters have been added in this edition, one on the reduction of bleeding during operations and the other on therapeutic aspects of anaesthesia and analgesia. The first is a fair account of "controlled hypotension", which does not minimize its dangers. The second is a somewhat cursory chapter of four pages.

Additions have been made to many of the other chapters. It is not surprising that that on muscle relaxants, which occupied but two pages in the first edition (January 1947) and eight in the second, has now grown to fifteen. What is surprising is that the chapter on spinal analgesia has not diminished, but increased. It occupies twenty-seven, thirty-three and forty-five pages in three succeeding editions. That the chapter on this subject should have been allowed to contribute so much to the general increase in size is perhaps out of keeping with modern thought in this country. There are one or two other subjects on which an opportunity to economize has not been taken. For instance, two and a half pages are still devoted to bromethol as they were in the first edition.

This edition has been improved by new illustrations, but one or two of the older ones, depicting little-used apparatus, might with advantage have been omitted.

The book is astonishingly accurate, and very up to date, though it is no longer correct to say that morphine has not been synthesized. Perhaps wisely, "hibernation" is not included, but N-allyl-normorphine has a place, and so have the newer synthetic analgesic drugs.

The index is a full one, and this is an important point in a book so packed with material.

The examination candidate will find this edition as useful and rewarding as its predecessors, and more senior anaesthetists will derive profit and pleasure from its pages. The book is well produced, but its appearance is somewhat marred by the fact that two very different kinds of paper are used in it. *Ronald Woolmer*

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 281)

GENERAL REMARKS ON INHALATION

INHALATION is simply the act of breathing, or at least so much of it as consists of inspiring, or drawing the air into the lungs. The term is usually applied when any medicinal substance is added to the air which the patient breathes, and the process is altogether different from that called "smoking," as practised by the nations of western Europe and of America, where the fumes of tobacco are merely drawn into the mouth and puffed out again. The eastern nations, however, always inhale when they smoke, as was stated before (page 274). This process of inhaling smoke, as I first witnessed it in a gentleman connected with one of the eastern embassies to this metropolis, is very instructive, as showing that the lungs become emptied of their contents by three rather full expirations and inspirations. When this gentleman took the cigar from his mouth to speak, the smoke could be seen issuing thickly with each word till there was a momentary pause as he took a fresh inspiration, then the smoke could be seen issuing with each word as before, only not so thick, and after another inspiration, the smoke could be still perceived in the expired air, but in a very diluted state; but after a third inspiration, it could no longer be seen till he had resumed the cigar.

The following are the chief reasons for resorting to inhalation.

1. Certain agents, as nitrous oxide and oxygen, being permanently in the gaseous form, cannot be administered in any other way.

2. By taking advantage of the immense surface of the air cells of the lungs for absorption, a more sudden and profound effect may be produced by medicine than it would be safe, or, in some cases, even possible to produce in any other way. It is to this circumstance, and to the rapidity with which certain volatile medicines exhale in the breath, and leave the patient free from their effects, that the power of preventing the pain of surgical operations is due.

3. Many medicines which have a disagreeable taste—as turpentine, creasote, and camphor—are not unpleasant when inhaled in the form of vapour; and the process of digestion is less interfered with than by taking them into the stomach.

4. Medicines, such as benzoic acid, and some of the gum-resins, which are believed to exert a local action on the mucous mem-

brane of the air-passages, may be expected to have a greater effect when inhaled, than when they are taken into the stomach in the same doses, and reach the lungs only through the circulation.

5. Some agents, as chlorine and ammonia, have a local action when inhaled, which they could not exert if exhibited in any other way.

In every kind of inhalation, the breathing should be allowed to go on freely, and in the natural way.

Medicines may be inhaled either at the ordinary temperature, or with the aid of artificial heat; and in the latter case they may be breathed with the addition of vapour of water, or with only so much of it as is naturally present in the atmosphere. The medicines in use for the prevention of severe pain, are always inhaled at the ordinary temperature.

CHLOROFORM

History and Composition. Chloroform was first made in 1831 by two chemists who operated independently of each other. The liquid, which is formed by the union of equal volumes of chlorine and olefiant gas, and which is usually called Dutch liquid, was named chloric ether by Dr. Thos. Thomson (*System of Chemistry*, 6th ed., 1820). In consequence of a statement in Silliman's *Elements of Chemistry*, that the alcoholic solution of this chloric ether was useful in medicine as a diffusible stimulant, Mr. Guthrie, an American chemist, attempted an easy method of obtaining it.* He distilled together chloride of lime and alcohol, and he considered that the product he had obtained was an alcoholic solution of the chloric ether of Dr. Thomson,† and it is still used in medicine under that name. About the same time, M. Soubeiran distilled together the above ingredients in France, and analysed the chloroform which he obtained. His analysis, which was incorrect, led him to name the liquid bichloric ether.‡ In 1832, Liebig examined the liquid which has been since named chloroform, but as he failed to detect the hydrogen which it contains, he called the liquid chloride of carbon,§ a name which its alcoholic solution occasionally bore afterwards when used as a medicine. In 1834, Dumas examined this liquid. He proved that Soubeiran and Liebig had not obtained it pure, or had been incorrect in their analysis.‖ He showed that it consists of two atoms carbon, one atom hydrogen, and three atoms chlorine.

Dumas gave the name of chloroform to the liquid, on account of the relation it bears in composition to formic acid, which consists of two atoms carbon, one hydrogen, and three oxygen.¶ Liebig, who, in common with other chemists, admits the accuracy of Dumas' analysis, has proposed the name of perchloride of formyle.** He supposes that the carbon and hydrogen which enter, in the same definite proportion, into numerous compounds, form a base which he calls formyle; and although this base has never been obtained in a separate form, its existence is well supported by analogy, and the term

* Dr. Pereira in Pharmaceutical Journal, March 1846, vol. v, No. 9.

† Silliman's American Journal of Science and Art, vol. xxi, p. 64, Jan. 1832.

‡ Ann. de Chim. et de Physique, t. xlviii, p. 131.

§ Ibid., t. xlix, p. 146.

‖ Ibid., t. lvi, p. 134.

¶ Formic acid is so named because it was originally obtained from the red ant (*Formica rufa*). It is now made from starch.

** Turner's Chemistry, 8th ed., p. 1009.

formyle is useful in assisting the memory to retain the composition of a number of substances. For all practical purposes, however, the medicine we are considering is likely to go by the name of chloroform. In the last edition of the London Pharmacopœia, the article has received a name intermediate between the other two. It is called chloroformyl, a name which departs from the brevity of the word chloroform, without having the merit of expressing the chemical constitution of the substance. I believe that no one uses the word chloroformyl; not even the Fellows of the College of Physicians in their individual capacity.

Mode of Preparation. Chloroform can be obtained in various ways, but the most convenient process, and the one which yields it in greatest purity, is that alluded to above, by which it was first procured. The following are the directions in the London Pharmacopœia for making it.

"Take of chlorinated lime, lb. iv; rectified spirit, Oss; water, Ox; chloride of calcium, broken in pieces, 3j. Put the lime first mixed with the water into a retort, and add the spirit to them, so that the mixture may fill only the third part of the retort. Then heat them in a sand-bath, and as soon as ebullition begins, withdraw the heat as quickly as possible, lest the retort should be broken by the sudden increase of heat. Let the liquid distil into the receiver so long that there may be nothing which subsides, the heat being reapplied if necessary. To the distilled liquid add a quarter of the water, and shake them all well together. Carefully separate the heavier portion which subsides, and add the chloride to it, and frequently shake them for an hour. Lastly, let the liquid distil again from a glass retort into a glass receiver."*

Some manufacturers of chloroform prefer to rectify it from dry carbonate of potassa, since they consider that it is liable to get an acid reaction from decomposition of the chloride of calcium, when it is distilled from that substance. The truth is, however, that there is very little occasion to use either of these substances; for the small quantity of water which chloroform can hold in solution is of no consequence.

Chemical and Physical Properties. Chloroform is a clear colourless liquid, having a hot and intensely sweet taste. It is not inflammable, but when paper moistened with it is introduced into the flame of a candle, it is destroyed with the evolution of smoke and chlorine gas. It is just half as heavy again as distilled water. Its specific gravity was formerly stated to be 1.483, but the liquid used for inhalation of late years has been heavier than this. I find that pure chloroform, when saturated with water, has a specific gravity of 1.500 at 60° Fah.; and after agitating it with sulphuric acid, to deprive it of the water, the specific gravity is 1.503. The amount of water that chloroform can hold in solution is only one part in from 200 to 300; and when this is separated by oil of vitriol, the chloroform is liable to undergo spontaneous decomposition.†

* Nearly all the chloroform used in Great Britain and her colonies is made in Edinburgh, where the spirit duty is lower than in England. The London druggists have almost ceased to make it, as they find it cheaper to get it from the trade in Edinburgh.

† The Edinburgh druggists suffered a great loss in 1850 from purifying their chloroform in this way on the recommendation of Dr. Gregory, who was not aware of the consequences, although they had been stated by Dumas (*Ann. de Chim. et de Physique*, t. lvi, p. 117).

Chloroform is soluble in alcohol and ether in all proportions, but it is very sparingly soluble in water. It has been said to require 2000 parts of water for its solution, but this is an error. As the solubility of this and similar medicines in watery fluids has a very important connexion with their physiological action, I took great pains to ascertain the solubility of chloroform correctly. By admitting small quantities of water into graduated jars containing chloroform vapour, I was able to ascertain that chloroform is soluble in about 288 times its volume of water. Chloroform is itself an active solvent of many bodies; dissolving camphor, caoutchouc, gutta percha, wax, resin, iodine, and some other substances very readily. It is a very mobile liquid, and when dropped from the lip of a small phial, the drops are very small. There are three drops to a grain of the liquid, and as a minim of it weighs a grain and a half, there are nine drops in two minims. Consequently persons should not speak indiscriminately of drops and minims, as they sometimes do, when talking of chloroform.

Adulterations. The odour of chloroform is by no means disagreeable. The only liquids that resemble it in smell are Dutch liquid and the chlorinated products of hydrochloric ether, but as they are much more difficult to prepare than chloroform, they are not likely to be substituted for it, or used for its adulteration. The smell of chloroform is therefore a good criterion of its purity and identity. When dropped on the hand, it should quickly evaporate, leaving not the least moisture or smell behind. If a disagreeble odour remains on the hand after the evaporation of the chloroform, it has probably been made from impure spirit, or even from wood spirit or acetone, and is unfit for medicinal use.* When chloroform becomes decomposed from any cause, it acquires a greenish-yellow colour, and gives off chlorine and hydrochloric acid, so that the alteration is at once apparent. When chloroform is pure it has no reaction on test-paper, but is quite neutral. The best way to detect a small quantity of hydrochloric acid in it, is to moisten a slip of blue litmus paper with distilled water, and hold it just within the neck of the bottle exposed to the vapour. If sulphuric acid should be present, it may be discovered by agitating the chloroform with distilled water, and adding nitrate of baryta.

The only article that can be mixed with chloroform without altering its appearance and smell is alcohol. This can be detected by the reduction it occasions in the specific gravity of the chloroform; or, if it be present in any considerable quantity, it may be discovered by adding water to a little of the chloroform in a graduated tube or measure, when a diminution of its volume takes place, owing to the water abstracting the alcohol. The chloroform also acquires a milky opacity under these circumstances. M. Miahle† speaks of the milky opacity of the chloroform on the addition of water as a very delicate test of the presence of alcohol; but I find that it requires upwards of two per cent. of alcohol to cause this appearance on the addition of water.

It has been asserted, and often repeated,

* I have seen some specimens of chloroform that left a white, limy-looking stain on the hand, which I believe was a minute quantity of crystalline chloride of carbon. These specimens were unobjectionable for all practical purposes, and had the merit of keeping remarkably well.

† See Med. Gaz., vol. xl, p. 1092.

that the presence of alcohol in chloroform causes it to have caustic properties, and makes its vapour unusually irritating. I have never seen any evidence of this, although I have had hundreds of opportunities of witnessing the action of chloroform mixed with spirit. Under certain circumstances, it is advisable to dilute chloroform with alcohol previous to its administration, as will be explained hereafter.

The chloroform I have met with in London has always been sufficiently pure for inhalation, except in a few cases where a small quantity had become decomposed, probably from having been left a long time exposed to strong daylight. In these instances, its altered appearance generally prevented its being used. I am not aware of serious consequences having arisen anywhere from the impurity or adulteration of chloroform. A case occurred in the London Hospital, where cough and a feeling of suffocation were caused by hydrochloric acid with which the chloroform was contaminated, but the inhalation was discontinued, and no ill consequences resulted.*

Chloroform should be kept in well-stoppered bottles, and protected from the light. It boils at 140° Fah. under the ordinary pressure of the atmosphere. It is consequently one of the most volatile liquids employed in medicine. with the exception of sulphuric ether and amylene.

The Vapour of Chloroform is more than four times as heavy as atmospheric air. It has a specific gravity of 4.2 at 60° Fah. Under ordinary circumstances, the vapour of chloroform has of course no separate existence, but is always mixed with air. It can exist in a pure state only when the temperature is raised to 140° or upwards; or when the pressure of the atmosphere is in a great measure removed by the air-pump. The quantity of vapour of chloroform that the air will hold in solution at different temperatures, under the ordinary pressure of the atmosphere, depends on the elastic force of the vapour at these temperatures. It is governed by a law precisely analogous to that which determines the amount of watery vapour which air will hold in solution.

The following table shows the result of experiments I made to determine the quantity of vapour of chloroform that 100 cubic inches of air will take up, and retain in solution, at varous temperatures.

Temp. Fah.	*Cubic inches*
40°	7
45	8
50	9
55	11
60	14
65	19
70	24
75	29
80	36
85	44
90	55

In the above table, the air is a constant quantity of 100 cubic inches which becomes expanded to 107, and so on; but it may be convenient to be able to view at a glance the quantity of vapour in 100 cubic inches of the saturated mixture of vapour and air, at different temperatures, and in the table which follows the figures are so arranged as to show this.

* Dr. Letheby in Med. Gaz., vol. xlvi, p. 1037.

Temp. Fah.	*Air*	*Vapour*
40°	94	6
45	93	7
50	92	8
55	90	10
60	88	12
65	85	15
70	81	19
75	78	22
80	74	26
85	70	30
90	65	35

As the effects of chloroform when inhaled depend entirely on the quantity of vapour present in the air which the patient breathes, the effect of temperature on its volatility is of great practical importance. The air, it is true, does not become fully saturated with vapour during the process of inhalation, but the effects of temperature are relatively as great. If, for instance, a person inhales chloroform from a handkerchief or inhaler, in such a way that the air he breathes shall be half-saturated with the vapour, then supposing the temperature of the apartment, the handkerchief, etc., to be 50°, the air he breathes will contain 4 per cent.; but if the temperature be 70°, the air will contain 9.5 per cent. of the vapour.

A considerable amount of caloric becomes latent during the evaporation of chloroform and the temperature of the vapour and air which the patient breathes are generally reduced a good deal, but not to the same extent as during the inhalation of ether. In giving chloroform from a small sponge which had been squeezed out of water, I have sometimes observed, after laying it down, that it became covered with a kind of hoar frost; the minute particles of frozen water having a slight taste of chloroform. The cold produced by the evaporation of a liquid like chloroform is often the means of checking the evaporation to a certain extent, and limiting the amount of vapour which is taken up by the air.

(*To be continued*)

SOUTH AFRICAN COUNCIL FOR SCIENTIFIC AND INDUSTRIAL RESEARCH

Bursary for Research into Causes of Anaesthetic Deaths

Applications are invited from medically qualified persons for a bursary of £1,000 to undertake full-time research into the causes of anaesthetic deaths. Knowledge of statistics a recommendation.

Bursary is initially for one year but may be renewed for a further two years. The bursar will work in Pretoria and Johannesburg.

Applications giving full information to reach Secretary/Treasurer, C.S.I.R., P.O. Box 395, Pretoria, by September 30, 1954.

ANNOTATIONS

REBREATHING IN ANAESTHETIC CIRCUITS

As with so many other methods used in anaesthetic practice, rebreathing has had its ups and downs. While John Snow carefully avoided rebreathing by unidirectional valves in the facemask of his famous Ether Inhaler of 1847, Roux in France popularized a primitive "nosebag" inhaler, to be followed 30 years later by Clover's Regulating Ether Inhaler—a rebreathing device *par excellence*.

The meaning of the term seems clear enough: "The re-inhalation of air or gases expelled during the preceding exhalation . . . may be total or partial" (Clement, 1951); however, there is a bewildering variety of procedures which have to be classed "rebreathing" to various degrees. Not everyone may agree with all details of Moyers' (1953) nomenclature for Open and Closed Systems, but it has the merit of pleading for more careful assessments of the degree of rebreathing in various apparatus.

Any facemask and other external apparatus introduces some "mechanical" dead space on the top of the "physiological" dead space, which is about 150 ml. for quiet breathing. Quite moderate "mechanical" dead volumes may lead to large CO_2 concentrations in the inspired gases (Conroy, 1943). Under a simple mask for open drop ether, the O_2 concentration may be appreciably below that of the outer air, quite apart from the diluting effect of anaesthetic vapours (Faulconer, 1949).

For many decades the use of "semi-closed" systems for administration of N_2O/O_2/ether in apparatus similar to Boyle's (1917) has spread throughout the anaesthetic world with relatively few investigations into the composition of the inspired mixtures. On the other hand, the somewhat related problem of O_2 and CO_2 concentrations in *absorber* systems has been the subject of numerous publications. The inspired O_2 concentration may fall dangerously below that of the fresh gases when using a semi-closed absorber technique (e.g. Foldes, 1952; Swartz, 1953). Furthermore, unexpectedly high CO_2 concentrations may occur in the inspirations and remain unnoticed by the anaesthetist (Mousel, 1946); consequently much attention has been paid to the characteristics of soda lime canisters (e.g. Walls, 1950).

A new investigation by Robson and Pask (this issue, p. 333) shows that careful packing of the normal canister cannot always be relied on to prevent channelling. It appears that a canister on its side may permit a very early break-through of high CO_2 concentrations unless the granules are kept suitably compressed.

The first quantitative study of rebreathing in a semi-closed system without absorber (Boyle's apparatus with Magill attachment) was published in this journal by Molyneux and Pask (1951). With simplified assumptions on respiratory flow pattern etc., the "rebreathed volume" could be expressed as a function of respiratory minute volume (RMV) and of fresh

gas flowrate (F) alone. In experiments with a mechanical lung the "backflow" of expirations into the breathing tube before opening of the valve was found to agree closely with the predictions of the simple theory. Some of the conclusions were: raising the supply to F = RMV may still admit of appreciable rebreathing; further increase of (F) to 2 × RMV would strictly exclude any rebreathing.

The theory of rebreathing is now extended to a variety of systems without absorber and also much refined by the mathematical work of Mapleson (this issue, p. 323). The Magill attachment is discussed in great detail ("System A") and the results seem at first sight very different from those just mentioned. A value of (F) slightly above the "effective minute volume" of the patient is said to prevent in practice any rebreathing of contaminated gases. This quantity (EMV = RMV − dead sp. × resp./min.) can be considered as the effective ventilation of the lungs and may be obviously much smaller than RMV (Orton, 1952). The divergence of the two theories seems less formidable when discriminating between "backflow" and "rebreathing of contaminated gases". Assume inspiration and expiration to be of equal duration; the *average* inspiratory flowrate is then 2 × RMV. Whenever the inspiratory flow momentarily exceeds (F), the deficit will be made up from the bag. Any "backflow" of the following expiration into breathing tube and bag is avoided if the bag volume at the end of the inspiration is the same as at the start; this can be ensured by making F = 2 × RMV. The main difference of opinion seems to be related to the permissible amount of backflow and the proportion which can be rebreathed without contaminating the inspiration with alveolar gases. Mapleson's most economical F = EMV is based on the assumption of uncontaminated dead space contents and the absence of any mixing in the breathing tube; if mixing occurs (F) would have to be raised but could still be less than RMV. An early, qualitative discussion of rebreathing in similar systems by Wynne (1941) had also led to fairly low values for an adequate supply (F). The effect of bag, expiratory valve and their relative positions on the degree of rebreathing has been discussed repeatedly (e.g. Foregger, 1929). The new investigation has now successfully included the characteristics of the various components into a comprehensive mathematical analysis; the general result for "System A" is that rebreathing is always prevented by values of (F) not above and usually well below RMV.

Woolmer and Lind (this issue, p. 316) make an interesting experimental contribution to the problem of rebreathing in some of these systems. Instead of measuring the backflow, the authors analyse the actual CO_2 concentrations in the inspirations of an artificial lung connected to the anaesthetic apparatus. Comparison with any theory requires some convention on a permissible amount of rebreathing, and an arbitrary maximum of 0.2 per cent CO_2 might not seem unreasonable. From the measurements on "System A" it would appear that values of (F) not far above EMV are already adequate. How closely the experimental conditions simulate those in practice—particularly with respect to mixing of contaminated gases—remains an open question. Other measurements

relate to *Ayre's T-piece* with a large tube connected to the expiratory limb; it corresponds to "System E" of Mapleson's article. The trend of the results agrees with the theoretical conclusions: (F) must be chosen more than twice as large as for "System A"; actually its value has to exceed 2 × RMV.

Preoccupation with these semi-closed systems must not obscure the simple fact that rebreathing can be abolished by the insertion of a one-way valve into the end of the breathing tube; the supply must be F = RMV. This procedure appeals to many who wish to prevent rebreathing with certainty and at reasonable cost (Ruben, 1953). This arrangement works well clinically provided that the valves are efficient (Baumgarten, 1954).

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AMERICAN SHADOW OVER THE RELAXANTS

In a recent article based on a survey of great size and complexity Beecher and Todd (1954) have made a unique contribution to the study of anaesthetic deaths.

In each of ten university hospitals in the United States a team consisting of a surgeon, an anaesthetist and a secretary worked for five years (1948–52) collecting data on no fewer than 599,548 anaesthesias. *All* deaths on all the surgical services were examined and categorized in the institutions where they occurred, and reports sent to a central office at four month intervals. The cause of death was characterized as due to the patient's disease, error in diagnosis, error in surgical judgement, error in surgical technique, or anaesthetic death. The latter was subdivided into deaths due primarily to anaesthesia, and those in which anaesthesia was an important contributory factor.

The primary anaesthetic death rate was 1 : 2,680, the overall anaesthetic death rate 1 : 1,560. From this it was estimated that, in the country as a whole, there were over 5,000 anaesthetic deaths each year. Death from anaesthesia is thus of sufficient magnitude to constitute a public health problem. Anaesthesia kills several times as many citizens each year, in the United States, as does poliomyelitis.

Even in a series as large as this it was

impossible to get an accurate statement of the death rate for a specific agent when many were used together, according to current custom, unless the rates differed by several hundred per cent. But this was so in the case of the muscle relaxants, the data relating to these drugs providing one of the outstanding features of this remarkable survey.

There were 384 anaesthetic deaths altogether. In 266 of these no muscle relaxants were employed, a death rate of 1 : 2,100. In 118 deaths a relaxant was used, a death rate of 1 : 370. " Here, then, in the simplest terms, we have a situation where so far as we have been able to see, one factor has been changed and the death rate has been increased nearly six fold ". The authors emphasize that there is no need to give undue mathematical emphasis to this actual figure, but rather to note that something serious appeared to happen when a relaxant was added to the situation.

The data show that these drugs were not reserved for difficult cases, or bad risks, or their use limited to major surgery. Although nurse anaesthetists, residents and specialists were involved there was no evidence that experience or training protected from disaster (nurses gave one-fifth of all the anaesthetics in these university hospitals, twice as many as the specialists). Gross errors in anaesthetic management occurred nearly twice as often in the relaxant group, but were such a low percentage of the total as not to influence the results to any great degree. An inherent toxicity is suggested, not a selective killing of the bad risk patient.

According to the data the combination of relaxant and thiopentone is not as dangerous as the combination with ether or cyclopropane. An " ether-relaxant " combination was used on 2,000 occasions, there were 32 deaths, a ratio of 1 : 62. The comparable ratio for " thiopentone and/or nitrous oxide-relaxant " based on 38,100 cases was 1 : 670.

Cardiovascular failure, despite artificial respiration of a generally effective type, appeared to be the cause of death in 44 cases. Commenting on this the writers state that it has not heretofore been recognized that death from a relaxant can be other than respiratory. But no data are offered strictly relating to the role the covering anaesthetic agents may have played in this particular mechanism of death. During the five-year period there was a great and steady improvement in the incidence of death associated with thiopentone without relaxants. (1 : 720 in 1948; 1 : 3,400 in 1952), but the rate for relaxants, *all* uses with *all* anaesthetic agents remained more or less constant (about 1 : 370).

The writers emphasize that none of these items adds up to *proof* that a relaxant killed a single patient, but they are all in the same direction and suggest that relaxants may be causing trouble.

British advocates of these drugs may be somewhat dismayed by the findings so far enumerated. But dismay will be replaced by perplexity on reading that, whereas, out of 118 " relaxant " deaths 12 came under the category of gross errors in anaesthetic management, on reclassification in terms of the mechanism of death 74 out of the 118 were regarded as due to respiratory failure (hypoxia). It is very difficult to reconcile this with the previous conclusion that experience on the part of the

anaesthetist is of no value to the patient, in this connection. Is death due to respiratory failure after the use of a relaxant regarded as unpreventable? It is inadmissible to develop this argument in the absence of clinical details, and since, at the very outset, the authors explicitly state that the object of their study was to describe how things *are* (in the United States) and not how they could be, or even as they should be. In the end they themselves make clear what must certainly be our own feelings in the matter, the need for further enquiries of a limited and more controlled type, which would probably give better information on specific problems such as this. But, if they have convinced us that relaxants can sometimes kill in a manner against which we, as yet, can offer no defence, and their own analogy is that however skilfully arsenic is administered, beyond a certain dose it kills—here then is a challenge indeed!

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BOOK REVIEW

An Introduction to Electronics for Physiological Workers. By I. C. Whitfield. Published by Macmillan. Pp. 236; 227 illustrations. Price 18*s*.

As the author states in his foreword, the book is " not for those who hope, in an idle hour, to pick up something of electronics " nor is it entirely suitable for the physiologist who already possesses an advanced knowledge of electronics in physiology. Even readers with a moderately advanced (if rusty) knowledge would not need assiduously to read the first ten chapters, which deal with the subject in the same fashion as any elementary textbook of electricity and magnetism. However, the inclusion of these chapters is both desirable and necessary if the book is to succeed in its purpose as a guide for " graduate students and others wishing to use electrophysiological technique ", and in this it succeeds admirably.

There is a great deal of general practical information in the second half of the book, which so often has to be acquired " the hard way ". Perhaps a chapter or two concerning practical laboratory layout, and the construction and support of electrodes may be missed by some readers. But one cannot please everybody, even in such an admirable book as this. It may be added that not the least attractive to many will be the clear style in which it is written, and the tacit assumption that the reader will not possess a high standard of mathematical knowledge.

T. G. Richards

CORRESPONDENCE

Sir,—My attention has been drawn to the Editorial appearing in the last issue of your Journal, wherein you discuss in detail the evidence submitted in the consolidated case of Roe and Woolley *v.* Minister of Health and another—the other being an anaesthetist.

May I respectfully submit the following observations on the views you have caused to be published.

I, like you, am uncertain that the truth relating to the *causa causans* of the unfortunate accidents described has in fact emerged, owing to the conflict of testimony presented by different witnesses, both expert and factual. The judge assumed that the introduction of phenol to the theca was the most likely explanation of the event that followed the administration of the spinal anaesthetics. There are experts, however, who have devoted much time and thought to the actual problems involved who would not subscribe to that view, just as there are experts who would not concede that the hazard of invisible cracks in ampoules is a reality. There are some who believe that the introduction of an infinitesimal quantity of phenol would not damage the cauda equina so grossly as was represented to have happened in this case, and that it would not establish the secondary inflammatory changes in the arachnoid that were believed to exist in both cases and were seen to exist in one. Perhaps, however, this interchange of views is largely academic as ampoules containing the anaesthetic employed in this case could—and probably in future will—be sterilized in an autoclave, as opposed to placement in a solution of phenol. It is said that the anaesthetic is stable and not likely to suffer any chemical change by sterilization in an autoclave.

It would be unfortunate for the public after reading the medical evidence, or indeed for anaesthetists who have not had the advantage of reading that evidence in full, were they to conclude that spinal anaesthesia is accompanied by greater hazards than other forms of anaesthesia. A conclusion of this order is not at present justified on the evidence available, but naturally anaesthetists will take care to ensure that any anaesthetic employed is not contaminated by some other substance likely to damage the nervous mechanism. The pendulum may have swung too far to the other side and I would enter a caveat against any pronouncement that either the public or anaesthetists in their representative capacities should exclude the use of spinal anaesthetics in suitable cases.

I am disturbed, however, at your comments with regard to the increasing tendency to litigation which is embarrassing the medical profession. You postulate that the medical defence societies will be unable to cope with the increased wave of medical litigation. This, frankly, is untrue. We are able to cope with the present wave and we would be able to cope with even a greater wave, were it to envelop the profession as you think might prove to be the case. At the moment the

members of defence bodies are called upon to pay a subscription which is minimal in size and sufficient only to meet the financial obligations that are calculated to be encountered. Should it transpire that the subscription has to be increased by 50 per cent or 100 per cent there are few, if any, who would raise objection. The indemnity afforded, the protection given, the settlement of cases out of Court when a defence is not available, and the comfort provided by the knowledge that the defence bodies are standing by, ready to assist whenever necessary, are of such practical value that prudent practitioners could not contemplate practising their profession without membership of a defence body at any reasonable cost. We do not desire to see our members hesitating to give patients what they consider to be the best and the most appropriate form of anaesthesia or treatment by virtue of a fear of ensuing litigation. That this fear will arise every now and again cannot be gainsaid but that it should vitiate or influence the judgement of practitioners is to be deprecated. The defence bodies can assure their members on the absence of the need for any anxiety concerning their financial or professional protection now or in the future. If financial re-arrangements are necessary these can be effected without hardship to anyone. We hope that anaesthetists and other practitioners will not fail to provide their patients with what they believe to be the best form of treatment merely because a few plaintiffs have been successful in establishing the existence of negligence in certain circumstances.

Finally, it would be no solution to the problem to arrange that the patient should be insured since, even were he insured against the hazard of anaesthesia, it would still be open to the insurer in suitable cases to argue that the anaesthetist had been negligent in the conduct of his work. A parallel is to be found in road traffic accidents today, where the State insists upon motorists being insured against certain risks. That, however, does not prevent the Insurance Company from litigating when necessary. The only solution to this problem by which we are confronted is the exercise of a reasonable degree of care and skill on all and every occasion when we undertake the responsibility to advise or treat a patient for a condition from which he is suffering.

ROBERT FORBES,
Secretary
(*The Medical Defence Union*)

EDITORIAL NOTE

NO-ONE is likely to be more cognisant and truly appreciative of the great service which has been, and is being, rendered by the Medical Defence Societies, than the readers and Editors of this Journal. It is reassuring to hear from Dr. Forbes that there is no fear of this aspect of litigation getting beyond their capacity. Our suggestion was, and remains, that some form of insurance for patients by avoiding chancy litigation might prevent unnecessary suffering and indignity for medical men who are only doing their best, while ensuring that patients who suffer accidental damage will have at least the mitigation of financial assistance for themselves and their families.

Regional Block. By Daniel C. Moore. Published by Charles C. Thomas, Illinois. Pp. 373; 262 illustrations. Price £4 0*s*. 0*d*.

SINCE the appearance of Labat's classic volume in 1923, scarcely twelve months have passed without some new book appearing on the technique of regional anaesthesia. Superficially, this may seem inconsistent with the gradual disappearance of these techniques from the ordinary day to day work of the anaesthetist. However, a little thought may point to the conclusion that these two facts are closely related. The disappearance of frequent opportunities to practise, to teach, to demonstrate and for the student to learn these techniques has created a demand for clear, definitive and detailed descriptions. It seems probable that, no matter how innocuous general anaesthesia may become, the anaesthetist may yet from time to time be called upon to perform regional blocks, either for therapeutic reasons or in special circumstances when general anaesthesia is contraindicated, or the facilities are inadequate. It is probably true to state that no recent work has been really satisfactory for the anaesthetist who occasionally uses local anaesthesia, with the exception of the monographs emanating from Oxford, exemplary in their clarity and brevity. Certainly if the circulation of such a book depended on those who were likely to practise local anaesthesia frequently, the production would be most uneconomical. Therefore, from such a volume we require (*a*) basic information in regard to the anatomy of the parts concerned, and the pharmacology and toxicology of the drugs to be used; (*b*) crystal clear description without ambiguity and unnecessary wordiness; and (*c*) a balanced emphasis on the dangers and difficulties which are likely to be encountered.

The volume under review fulfils these criteria. The anatomical descriptions are ample without, as has been a tendency in some recent books, converting the work into a textbook on anatomy. Pharmacology is scrappy, but just adequate for the practising clinician, and the techniques (mercifully only one for each procedure) are adequately described without that obscurity in respect to angulation and corporeal planes which is characteristic of this type of literature. Probably the 3-D technique exemplified in a recent paper (Pask, 1954) will revolutionize this type of description in the future—this present effort will certainly suffice for the present.

Very few medical authors will get by without provoking some criticism from their reader colleagues, although such criticism will inevitably vary from individual to individual. Here, perhaps, a general disapproval will be expressed for the disgusting practice which is suggested to enable the practitioner to distinguish local anaesthetic solutions from alcohol, ether, or other sterilizing fluids. Apparently Dr. Moore likes to

spray some of the solution which he has aspirated into the syringe on to his mask before injection, and thereupon taste it on the mask!

Times change, and the truly scientific mind must ever be a Nietscheian "yea-sayer" to progress and therefore, although horror is the instinctive reaction to expressions such as "each patient must be individualized" or "walking the rib", one appreciates that they are brief and accurate descriptions and therefore, one supposes, they must be accepted. The writer certainly hopes and believes that an unjustifiable reflection is made on the overall standard of American specialists in "anesthesiology" by the author's preface which declares that " . . . it is not uncommon to find physicians, even specialists in anesthesiology, who do not realize that Pentothal is the trade name for thiopental, that Nembutal is the trade name for pentobarbital, that Pontocaine hydrochloride is the trade name for tetracaine hydrochloride and that Novocaine is the trade name for procaine hydrochloride." We believe that the author has played safe by quoting both the proprietary and the American official names, and also by giving dosages in both the English Apothecaries and Metric Scale.

This is a book to be recommended without hesitation to the occasional regional anaesthetist who, having purchased it, should never need to buy another—unless he is tempted probably as much by the novelty as by the utility of a future production in 3-D.

Cecil Gray

REFERENCE

Pask, E. A., and Robson, J. G. (1954). *Anaesthesia*, **9**, 94.

Spinal Epidural Analgesia. By P. R. Bromage. Published by Livingstone, Edinburgh. Pp. 132; 47 illustrations. Price 15*s*.

Anaesthetists, whether particularly interested in epidural spinal analgesia or not, should find much food for thought in this short work on the subject. It raises a number of points on which we shall no doubt agree to differ, hence the interest.

The author has been extraordinarily successful in the practice of this technique; a failure rate of only $1\frac{1}{2}$ per cent must be quite exceptional. There are chapters on epidural pressure, the means of identifying the space, drugs used and equipment required, and on continuous epidural spinal analgesia. The author regards the latter as a slow-going subarachnoid analgesia due to the diffusion of the injected fluid from the epidural to the subarachnoid space.

It is to the remarks on blood pressure that I imagine some of us will find it difficult to subscribe. It is stated that "Vascular tone is maintained directly by the vasomotor nerves emerging in the sympathetic outflow between the first thoracic and the second lumbar segments" and that a fall of blood pressure may therefore be expected in proportion to the segmental involvement. As the vasoconstrictor nerves emerge in the anterior roots, the fall of blood pressure depends on the number of *anterior* roots involved, not on the segmental involvement which may be a very different thing, when the latter is assessed by the height of analgesia. Again, Bromage states that some authorities claim that epidural analgesia alters blood pressure very little, and disagrees with them.

He explains the divergence of opinion as being due to the presence or absence of consciousness in the patients Those who supplement epidural analgesia with a general anaesthetic find a fall of blood pressure, while those who rely entirely on the epidural do not. If 100 mg. of ephedrine be injected subcutaneously just prior to the subarachnoid injection of a 1 per cent solution of amethocaine (heavy) there is as a rule no fall of blood pressure until the exploration of the abdomen. It is my impression that this fall may be modified or even prevented by the injection of thiopentone intravenously, that is by the abolition of consciousness.

Few anaesthetists will agree with the author's statement on page 104: "Epidural block is to be preferred in all cases when subarachnoid analgesia might otherwise have been considered, since the avoidance of dural puncture eliminates *all possibility* of spinal headache or subarachnoid infection and the greater duration of epidural injections provides longer operating time." The italics in this quotation are mine and careful readers will realize that "all possibility" is somewhat extreme. Perforation of the dura is one of the accidents which occur, and as the analgesic solution penetrates the dura so also presumably may micro-organisms, in which case both spinal headache and meningitis are at least possible. But there are a number of positive advantages in subarachnoid analgesia which are not mentioned. It is more certain, definite and quicker; many an operation will be finished and the patient back in bed before the surgeon relying on epidural analgesia has been able to begin. In spite of the unusual success which the author has had, the number of failures is still three times as great as those to be expected under subarachnoid analgesia.

We may agree that "for therapeutic blocks where the duration of the blockade must be measured in days" the epidural route is likely to find its most suitable field for action.

The book is on good paper well illustrated and printed. There are very few mistakes, the only one I noticed on page 75 line 5 has "diplaces" instead of the more usual form "displaces".

E. Falkner Hill

FACULTY NEWS

THE Council of the College, acting on the recommendation of the Board of Faculty, has appointed the following Examiners for the ensuing year:

PRIMARY EXAMINATION, F.F.A.R.C.S.

Anatomy:	Professor Gilbert Causey
	Professor James Whillis
Physiology:	Professor David Slome
	Professor W. R. Spurrell
Pharmacology:	Professor C. A. Keele
	Dr. Halley C. Stewart
Pathology:	Professor Geoffrey Hadfield
	Dr. G. D. Lumb

FINAL EXAMINATION, F.F.A.R.C.S.

Medicine:	Professor Alan Kekwick.
Surgery:	Mr. A. Hedley Whyte
Anaesthetics:	Dr. Frankis T. Evans
	Dr. T. Cecil Gray
	Professor R. R. Macintosh
	Mr. A. D. Marston
	Dr. B. L. S. Murtagh
	Professor W. W. Mushin
	Dr. G. S. W. Organe
	Professor E. A. Pask

D.A. EXAMINATION

Surgery:	Mr. Clive Edward Butler
Anaesthetics:	Dr. W. A. Low

THE following have been elected to the Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons:

Adams, A. K.
Armstrong, B. P.
Ashbery, A. W. H.
Asquith, E.
Baddock, G.B.
Ball, H. C. J.
Bardeen, Ann
Barr, J. T.
Baxter, R. W.
Bayles, O. H. E.
Beaton, D.
Bisset, May Simpson
Black, J. K.
Blades, H. R.
Bourke, J. D.
Boulton, T. B.
Boyd, W. H. F.
Brown, C. P.
Brownrigg, E. K.
Buck, H. A.
Buckley, R. W.
Bullough, J.
Bulow, J. E.
Burbridge, H. C.
Burgoyne, J.
Canter, D.
Capon, J. H.
Chambers, K. B.
Cheshire, P. S.
Chester, Mrs. A. M.
Chivers, E. M.
Clark, D. C.
Clement, L.
Coleman, E. R.
Condon, H. A.
Cooper, J. A. L.
Connell, R. F.
Crowley, T. F.
Currie, T. T.
Curtis, H.
Curtiss, E. S.
Dalgleish, A. T.
Danin, A.
Davenport, H. T.
Davenport-Jones, I.
Davidson, J.
Davies, D. G. H.
Doherty, W. F. O'M.
Edwards, E. M.
Edwards, H. V.
Elliott, J. R.
Everitt, Elizabeth Florence
Farquhar, J. K.
Fell, J. N.
Flett, E. H.
Forbes, D. A.
Foregger, R.
Forsaith, J. R.
Foster, M.
Fraser, A.
Fraser-Simpson, A. J.
Garden, M.
Garry, H.
Georgeff, N. H.
Gibson, E. McC.
Gibson, R. E.
Glynn, K. B.
Goetzee, Beryl Margery
Goldsmith, E.
Goodwin, G. P.
Gordon, H. E.
Gordon, J.
Gow, I. M.
Grace, A. H.
Gray, P. W. S.
Grenville, H.
Griffin, T. P.
Guerrier, S. M.
Halstead, D. B. I.
Hardy, H. M.
Harper, J. K.
Hart, W. S.
Hartley, Mary Jeannette
Havers, G. G.
Hellings, Pamela Mary
Herington, G.
Herron, R. A. C.
Hobbs, A. N.
Holborow, M.
Hopkin, D. A. B.
Hopper, G. R.
Howard, D. C.
Howell-Jones, H.
Hunt, B.
Hutton, J. N. T.
Jackson, G. A.
Johnson, P. D.
Johnson, G. J.
Jones, R. G. G.
Jones, W. K.
Kay, R. S.
Keates, G. H. W.
Keir, R. M. S.
Kenton, B.
Knowles, H. T.
Kuttner, M.
Kyles, J. R.
Lapraik, J.
Leaming, H. L.
Leatherdale, R. A.
Leibovitz, J.
Leighton, E. J.
Levis, R. D.
Lewis, W. J.
Linacre, J. L.
Littler, E. L.
Loder, R. E.
Loughrey, J. D.
Mandow, G.
McAlpine, D. F.
McDougall, B. A.
McEnery, J. J.
McGrath, G. D.
McIntyre, J. W. R.
MacKenzie, A. L.
McKenzie, R. M.
McVey, A. V.
Magner, T.
Marchant, J. M.
Marsden, Audrey
Mason-Walshaw, G.
Masson, A. H. B.
Matthias, J. Q.
Miller, A. A. McC.
Merlin, P. T.
Milner, E. A.
Moore, J.
Moore, P. H.
Morch, E. T.
Morgan, D. K.
Morgan, O. T. L.
Mosscrop, L. E.
Murdoch, J. G.
Murphy, J. P.
Murphy, O. J.
Oakenfull, B. G. P.
Ostlere, Mary
Parker, Barbara D.
Patrick, H. F.
Pearce, D. J.
Pegg, J. G.
Pelmore, J. F.
Piney, J. M.
Polland, J. J.
Potter, M. E.
Price, W. L.
Psaila, J.
Pyddoke, Mrs. S. W.
Rains, Kathleen M.
Ramsay, C.
Read, N. P.
Rees, L. T.
Rendell, C. M.
Richardson, J. C.
Richmond, M. McC.
Robertson, R. K.
Rooms, Margaret
Rushton, M.
Ruddell, J. S.
Samrah, M. E.

Scott, R. D.
Scott, W. E. B.
Searle, J. B.
Sheppard, R. G.
Simmons, P. H.
Simpson, A. D. H.
Sinton, E.
Sladden, Gillian Esther
Slowe, J. J.
Smith, A. E.
Smith, J. H. W.
Spears, J. R.
Stephen, E. D. S.
Stevens, W. J.
Stoneham, R.
Stuart, G. H.
Tees, J. E.
Thomas, Betty
Thorne, T. C.
Tin, U.
Trapps, N. C. B.
Vaughan, A. B.
Vellacott, W. M.
Walker, O.
Wallace, P. E.
Watson, W. R.
Watt, O. M.
Welsh, A. T.
Whitehall-Cooke, E. C.
Wilkinson, E. M.
Wilkinson, Edith Mary
Winstone, N. E.
Wordsworth, V. P.
Wright, A. P.
Wyant, G. M.

A THREE-WEEK Anaesthetics Course will be held from October 11 to 29, which will be similar to the one held this spring. A Pharmacology Course of 20 lectures will be held from November 29 to December 10. Details, application forms, etc., may be obtained on application to the Secretary.

THE NEW GREAT HALL AND COUNCIL ROOM

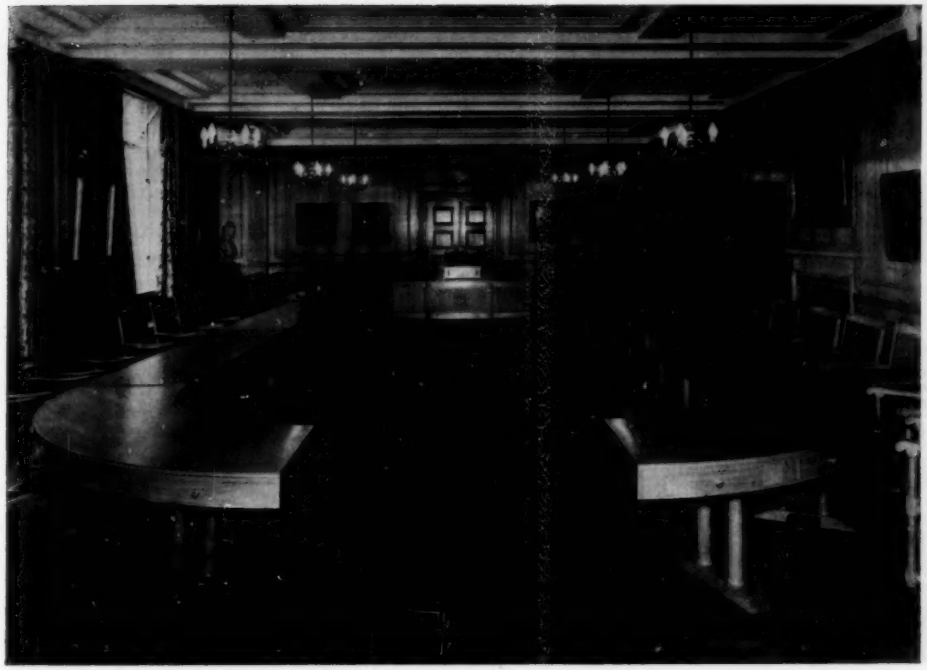
THE first public function to take place in the Great Hall was a Hunterian Lecture, given by Professor D. J. Browne. The first public function held by the Faculty in that Hall was the *viva voce* examination for the 2nd Final F.F.A.R.C.S., and this took place on May 3, 4 and 5.

The Hall was put to its first social use for the Reception for the American College of Surgeons on May 17. The Seventh Anniversary Dinner of the Faculty will be held there on March 23, 1955, and the Scientific Meeting was there on June 19.

BOOK REVIEW

The Medical Annual 1954, edited by Sir Henry Tidy and R. Milnes Walker. Published by John Wright. Pp. 524; 67 plates, 32 illustrations. Price 32*s.* 6*d.*

We take this opportunity to express our sympathy with Sir Henry Tidy, who has lost Professor A. R. Short, his companion editor for thirty-five years. As regards this edition, it is about the same size as that of last year. The editors in their introduction call attention to the various matters that have been of interest during the past twelve months, as for example, air pollution as exemplified by "smog" and the question of the relationship between carcinoma of the lung and tobacco smoking. Dr. C. Langton Hewer again writes the article on "Anaesthesia and Analgesia". Muscle relaxants, induced hypotension, hypothermia all receive short notice. Attention is drawn to some of the dangers inherent in modern methods of anaesthesia such as the use of cuffed intratracheal tubes and the apparent significant increase in the incidence of the regurgitation of stomach contents. An article on "Analgesic Drugs" by Professor Andrew Wilson leaves one with the impression that in spite of a great deal of work on synthetic drugs nothing has been found to replace morphia, and that is in accordance with one's own clinical experience. As usual, the *Medical Annual* of this year maintains its high standard and general usefulness. *E. Falkner Hill*



Council Room, Royal College of Surgeons.

Great Hall, Royal College of Surgeons.

FIRST BRAZILIAN CONGRESS OF ANAESTHETISTS

THE First Brazilian Congress will be combined with the Second Latin-American Congress of Anesthesiology and will be held in Sao Paulo, Brazil, from September 12 to 18, 1954.

The two principal themes of the Congress will be "Artificial Hibernation", the chief speaker being Dr. Gil Soares Bairao, Sao Paulo, Brazil, and "Anaesthesia for Cardiovascular Surgery", the principal speakers being Dr. Horacio Antonio Cabo and Dr. Alberto Gonzalez Varela, Buenos Aires, Argentina.

The President of the Congress is Dr. Luis Rodrigues Alves, the Secretary, Dr. Zairo E. G. Vieira and the Treasurer, Dr. Oscar F. Barreto. Other members of the Committee are Drs. Mario C. d'Almeida, Caio Pinheiro, Roberto de Araujo, J. A. Zugliani, Flaminio Camargo and J. Almeida Bello.

THE SOCIETY OF ANAESTHETISTS OF THE SOUTH-WESTERN REGION

A MEETING of the Society of Anaesthetists of the South-Western Region was held in Plymouth, on May 14–15, 1954. The following papers were read:

"Developments in Artificial Respiration and Respirators", by Professor E. A. Pask, O.B.E., M.D., B.CH., F.F.A.R.C.S.

"Hypothermia and Antihistamines", by Dr. John Beard, M.D., F.F.A.R.C.S.

"Respiratory Failure in Poliomyelitis and its Treatment", by Dr. D. F. Johnstone, M.R.C.S., L.R.C.P.

Theatre Sessions took place on the Saturday morning, during which there were demonstrations of artificial hibernation.

LIVERPOOL SOCIETY OF ANAESTHETISTS

Programme 1954–1955

1954		
October	29	Discussion on "The Use and Abuse of Thiopentone" to be opened by Dr. J. W. Dundee.
December	10	Dr. A. L. Stead: "The Role of the Liver in the Detoxication of Muscle Relaxants." Dr. S. Lipton: "Anaesthesia in Neurosurgery."
1955		
January	19	Dr. M. H. Armstrong Davison: "Of the Natural Part of Anaesthesia."
February	23	Short Papers by Registrars, Drs. B. J. Coyne, J. R. Cross, Betty McCarthy and H. McIntyre.
March	25	Joint Meeting with local division B.M.A.: "Anaesthesia and the General Practitioner."
April	21	Joint Meeting with Anaesthetic Section, Manchester Medical Society. Dr. M. W. Johnstone: "The Mechanisms of Cardiac Arrest." Dr. G. McLoughlin: "Haemostasis."
May	20	Annual General Meeting.
July	16	25th Anniversary Dinner.

Educational Supplement

September 1954

REVIEW ARTICLE

A REVIEW OF CHLORPROMAZINE HYDROCHLORIDE

BY

JOHN W. DUNDEE

Department of Anaesthesia, The University of Liverpool

IN the history of modern medicine there have been few drugs to which so many properties have been ascribed or which have found so many clinical uses as chlorpromazine. Almost 500 publications appeared within two years of introduction of the drug (Viaud, 1954) and a bibliography complete to the end of 1953 (Specia) lists 417 papers concerning chlorpromazine. Of these, 74 were devoted to its pharmacology, 160 to its use in anaesthesia and surgery, and the remainder deal with its use in, among other fields, obstetrics and gynaecology, pathology, paediatrics and psychiatry.

From this it will be apparent that any review of chlorpromazine which included all the publications would be of such a size as to make it of little value to readers. Most of the published literature deals with the use of chlorpromazine in combination with many other drugs and adds very little to our knowledge of the actions of the drug itself. In this review an attempt has been made to piece together and critically assess the most important papers which deal solely or mainly with chlorpromazine or which compare it with other similar drugs. It will be appreciated that, if the present rate of publications on chlorpromazine continues, such a review can never be quite up to date.

HISTORY

Chlorpromazine was synthesized by M. P. Charpentier working at the research laboratories of Rhone-Poulenc-Specia, Vitry-sur-Seine, in December 1950. Its synthesis resulted from a systematic study of the phenothiazine derivatives in an attempt to find a substance resembling promethazine, but with a more marked central depressant action (Rhone-Poulenc, 1954).

In the middle of 1951 chlorpromazine was first used by Laborit and Huguenard from Paris in their technique for "artificial hibernation" (Huguenard, 1953a), and its use in anaesthesia in combination with pethidine was reported by Laborit in January 1952 (Laborit, 1952). Delay and Deniker first described the value of chlorpromazine in psychiatry at the Congress of French-speaking Psychiatrists at Luxembourg in July 1952 (Lehmann and Hanrahan, 1954). The first

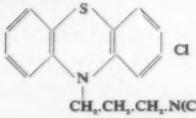
comprehensive report on its pharmacology was that of Courvoisier, Fournel, Ducrot, Kolsky and Koetschet which appeared in January 1953.

It was not until the end of 1953 that reports on chlorpromazine from this country appeared. These were concerned with its use in anaesthesia (Smith and Fairer, 1953) and in the production of hypothermia by surface cooling (Dundee, Gray, Mesham and Scott, 1953).

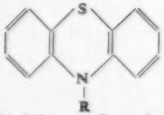
Chlorpromazine was first introduced as "4560 R.P." and the trade name "Largactil" was given to it in France. It appeared in this country as M & B 2378 and here also the trade name Largactil is used. A list of its synonyms in various countries is given in table I.

CHEMICAL AND PHYSICAL PROPERTIES

Chlorpromazine is a phenothiazine derivative, and can be represented by the following formula:



Chemically it is the hydrochloride of 3 chloro-10 (3-dimethylamino-n-propyl) phenothiazine. Its similarity to other phenothiazine derivatives in everyday use is shown below:



R = $CH_2.CHN.(CH_3)_2.HCl$ (with CH_3) — Promethazine hydrochloride (Phenergan)

R = $CH_2.CHN.(C_2H_5)_2.HCl$ (with CH_3) — Ethopropazine hydrochloride (Lysivane)

R = $CH_2.CH_2.N(C_2H_5).HCl$ — Diethazine hydrochloride (Diparcol)

Chlorpromazine is a greyish white crystalline powder with a slightly pungent odour. Its molecular weight is 355.3 and melting point 179–195°C. It is very soluble in water (1 g. in 2.5 ml.), methyl and ethyl alchohol and chloroform, but insoluble in ether and benzene. The pH of 5 per cent aqueous solution is between 4 and 5. Both the powder and solutions become discoloured in bright light, although this is not thought to impair their activity or increase toxicity.

A precipitate forms when chlorpromazine is mixed with any of the thiobarbiturates in clinical use. It is also precipitated by hexamethonium bitartrate, atropine sulphate, one brand of suxamethonium chloride (D.F. & Co.), 1.4 per cent sodium bicarbonate, 10 per cent saline, 30 per cent dextrose and Ringer's solution. The precipitate which forms when it is mixed with 2 per cent gallamine triethiodide dissolves in an excess of gallamine. A faintly cloudy solution results from diluting chlorpromazine with polyvidone, some solutions of normal saline and 5 per cent dextrose (depending on their pH). The drugs with which it may be mixed include d-tubocurarine chloride (Tubarine miscible), some makes of suxamethonium (Anectine, Scoline), pethidine hydrochloride, morphine hydrochloride, l-methorphinan, promethazine hydrochloride, adrenaline and nor-adrenaline, procaine and procaine amide, lignocaine, nikethamide, picrotoxin, ergometrine, desoxyephedrine and ascorbic acid. While one is not likely to mix chlorpromazine with many of the above drugs this information is worth bearing in mind should it be necessary to inject the solutions in succession through one of the non-blocking intravenous needles of the Gordh or Mitchell types.

TABLE I

Proprietary names and forms of presentation of chlorpromazine

Country	Trade Names	Presentation
British Isles	Largactil (M & B 2378)	Tablets, 10 and 25 mg. Ampoules, 50 mg. in 2 ml.: 25 mg. in 5 ml.
Germany	Megaphen	
Sweden	Hibernal : Largactil	
France	Largactil (4560 R.P.)	Tablets, 25 mg. Ampoules, 50 mg. in 2 ml.: 25 mg. in 5 ml. Guttae 1 mg. in 1 drop; bottles of 10 ml. Suppositories containing 25 mg. and 100 mg.
Remainder of Europe	Largactil	Tablets, 25 mg. Ampoules, 50 mg. in 2 ml.
U.S.A.	Thorazine (S.K.F. 2601—A)	Tablets, 10 and 25 mg. Ampoules, 50 mg. in 2 ml.
Argentine	Ampliactil	
Brazil	Amplictil	

Intravenous administration of chlorpromazine requires dilution with isotonic saline because of its relatively low pH and the danger of damaging the endothelium of the vessels. Deep intramuscular injection, while safer, is somewhat painful and for this reason Lehmann and Hanrahan (1954) advise diluting the drug with distilled water, saline or procaine.

PHARMACOLOGY

The amine derivatives of phenothiazine are a group of substances with an extremely complex action which has been investigated by many workers (Hutcheon, 1953; Burn, 1954; Friebel, Flick and Reichle, 1954). Among the properties that have been ascribed to them are a local anaesthetic action, ability to lower body temperature, reduce or abolish the vasoconstrictor action of adrenaline, inhibit salivary secretion induced by carbachol, inhibit acetylcholine induced contractions of isolated ileum and prolong the refractory period of cardiac muscle. In addition some of them exhibit anti-histamine activity and potentiate the action of narcotics (Winter, 1948).

Friebel et al. (1954) observed that the relationship between chemical composition and pharmacological activity which can be applied to other groups of compounds holds good for the phenothiazine derivatives, but they also found some relationships which were apparently only valid for this group of drugs. It was noted that the dimethyl amine derivatives had a more marked anti-histamine activity than otherwise similar diethyl derivatives. The propylamine derivatives, including chlorpromazine, were found to have a predominantly central point of action, while the

introduction of a chlorine atom into the phenothiazine nucleus of propylamine derivatives had little effect on the pharmacological actions.

Detection in Body Fluids.

Dubost and Pascal (1953) have described a method for the estimation of free and conjugated chlorpromazine in biological fluids. This is based on the fact that chlorpromazine causes a fairly sensitive reaction with sulphuric acid (S.G. 1.83). The chlorpromazine base is extracted with ether in an alkaline medium and then a salt is reformed which in the presence of sulphuric acid gives a carmine red coloration. This coloration is very stable and extremely sensitive, determination of quantities as small as 1: 800,000 being possible using Meunier's electrophotometer.

Fate in the Body.

The above workers have studied blood and urine levels of chlorpromazine in the dog and rabbit after various subcutaneous or oral doses. The maximum blood concentration occurred $1\frac{1}{2}$ hours after subcutaneous injection, while the peak level was not reached until 3 hours after oral administration. They found a close correlation between the dose and the blood concentration irrespective of the route of administration, suggesting that chlorpromazine is well absorbed from the alimentary tract. There was still an appreciable amount found in the blood (1.7 to 2.5 mg./litre) of rabbits 24 hours after administration of large oral doses (250–500 mg./kg.) while negligible amounts were found at the same interval after subcutaneous injection.

Analysis of the urine revealed that maximum renal excretion of the unchanged drug occurred 6 to 24 hours after administration. The urinary output of the drug falls very slowly during the next few days, but irrespective of the route of administration it never exceeds 8 per cent of the total dose administered. This suggests that there is a considerable breakdown of chlorpromazine in the body, but the site and method of detoxication are as yet unknown.

The observation of Moyer, Kent, Knight, Morris, Higgins and Handley (1954) that in patients with liver dysfunction the drug appeared to be more effective and sedation was more marked after oral administration, suggests that the liver is responsible for at least a part of its breakdown. In substantiation of this view is the finding of Lehmann and Hanrahan (1954) that half of their 71 patients who were on daily doses of chlorpromazine showed slight changes in cephalin-cholesterol flocculation, one-third showed changes in total serum protein values and albumin/globulin ratios, while three developed jaundice which appeared to be of toxic origin. Three further cases of jaundice following chlorpromazine have been reported by Winkelman (1954), in one of whom liver biopsy revealed previous chronic liver damage.

Effect of chlorpromazine on conscious subjects.

Following intravenous injection of 0.3–2 mg./kg. subjects become drowsy, calm, listless and apathetic. The skin is warm, dry and pale, especially the face; axillary, oral and rectal temperatures falling and extremity temperatures rising. A bilateral

Horner's syndrome appears within a few minutes. Subjects frequently complain of muscular weakness, cold and thirst. The pulse rate shows an early rise gradually settling to normal, but with wide fluctuations. The blood pressure is labile and varies with posture. Respiration is constantly depressed and dyspnoea may follow the administration of large doses (Couthier, 1953; Dobkin, Gilbert and Lamoureux, 1954).

Intramuscular injection of 25–50 mg. chlorpromazine causes sedation in about 50 per cent of cases, this symptom appearing within 15–30 minutes of injection and lasting from 4 to 6 hours. Often accompanying this is weakness, a feeling of cold, dryness of the mouth, myosis and faintness. This latter is due to an orthostatic fall in blood pressure, varying between 20–40/10–30 mm. Hg and accompanied by a compensatory tachycardia. The pulse rate settles down within 90 minutes, blood pressure remaining at a level about 20 mm. Hg below normal. Respirations are deep and regular (Ratschow, 1953; Anton-Stephens, 1954; Kent, Knight, Morris, Dizon and Moyer, 1954; Lehmann and Hanrahan, 1954). The same picture follows oral administration, save that the onset of symptoms may be delayed for 90 minutes after administration.

Larger oral or parenteral doses lead to motor retardation, an unsteady gait and a wooden facial expression resembling Parkinsonism. The degree of drowsiness is proportional to the dose, but although subjects may fall asleep they can be easily wakened (Lehmann and Hanrahan, 1954). They show a psychic indifference both to their surroundings and condition, loss of subjective anxiety and are occasionally euphoric (Anton-Stephens, 1954), but experiments show less impairment of tests of reaction time with chlorpromazine than with quinalbarbitone, despite the fact that in the doses administered chlorpromazine had the greatest sedative effect (Lehmann and Hanrahan, 1954).

With prolonged administration there develops an early tolerance to the sedative effect of chlorpromazine, the dose often having to be increased after the first 24 hours to maintain a constant degree of sedation (Ratschow, 1953). This does not apply to the tachycardia, blood pressure changes, and dryness of mucosa which frequently persists as long as the drug is continued. Muscular weakness is common and most patients complain of cold. The appetite remains good, but there is a tendency to constipation.

The mental effects of prolonged administration of chlorpromazine have been called "pharmacological frontal lobotomy" (Terzain, 1952). Patients show a lack of spontaneous interest in their surroundings, are generally immobile and at first glance seem to be heavily drugged. However the higher psychic functions are preserved to a remarkable degree and patients are capable of sustained attention and concentration. Lehmann and Hanrahan, (1954) summarize this effect thus, " . . . chlorpromazine is the only powerful sedative whose action is restricted to a selective inhibition of drive without producing disinhibition of effect at any level of dosage."

Central Nervous System.

The soporific action of chlorpromazine, already referred to in detail above, has

been convincingly demonstrated by intraventricular injection of 2 mg./kg. in the dog (Cathala and Pocidalo, 1952). This produced immediate anaesthesia with complete muscular relaxation, abolition of the corneal reflex and sphincter disturbances. The effect lasted for 1–2 hours and was followed by several hours of depression. Animal experiments have also shown that conditioned reflexes are depressed with sub-hypnotic doses of chlorpromazine (Archer, 1954; Beard, 1954). It appears from the studies of Dasgupta, Mukherjee and Werner (1954) that the central depressant activity of chlorpromazine and thiopentone increase after disconnection of certain cortical areas, the effect being greater with the former drug.

Electroencephalographic studies show that the overall effects of chlorpromazine are absolutely identical with normal sleep (Terzain, 1952). In contrast with the barbiturates which produce a rapid rhythm, independent of the state of wakefulness, chlorpromazine has no effect on the electroencephalogram if consciousness is not disturbed. In the state of disinterestedness there is an accentuation of the 'theta element' and other changes. The findings in patients with anxiety were parallel to their clinical improvement, alpha rhythm gradually reappearing. Awakening is as from a normal sleep. Terzain (1952) concludes that the effects of chlorpromazine represent depression of the reticular formation, particularly the sensory and autonomic spheres; the action is mainly of the afferent ascending portion, the afferent (sensory) side being only slightly affected. From an analysis of the effects of chlorpromazine on the central and autonomic nervous systems Aron (1954) has come to the conclusion that its site of action is probably in the hypothalmus.

The stimulant action of caffeine, amphetamine, nikethamide and nicotine are antagonized by chlorpromazine, but the convulsions of strychnine are unaffected (Courvoisier et al., 1953). The central depressant action is unaffected by amphetamine or caffeine and sodium benzoate (Dobkin et al., 1954). One patient to whom nikethamide was administered (in error) to counteract orthostatic hypotension developed a series of generalized convulsions, from which recovery took one hour (Lehmann and Hanrahan, 1954).

The central action of chlorpromazine is further demonstrated by its potentiating effect on the action of anaesthetic agents, sedatives and analgesics. Courvoisier et al. (1953) have demonstrated this effect on animals. After chlorpromazine sleep can be induced with smaller doses than normal of hexobarbitone, butobarbitone and ether (attributed to increased sensitivity of the cerebral cells) and there is a potentiation of the duration and depth of anaesthesia. Although devoid of analgesic activity of its own, chlorpromazine likewise potentiates the analgesic effect of morphine, pethidine and other weaker analgesics. Chlorpromazine potentiates the effects of alcohol. It modifies the signs of intoxication suppressing the excitement phase and causing sudden collapse. It prolongs the duration of narcosis and increases the toxicity.

Although no figures of the actual dose of anaesthetic agents administered are recorded in the literature, many observers have reported this potentiating effect of chlorpromazine, especially on thiopentone (Laba, 1953; Déchêne, 1954;

Dobkin et al., 1954; Rizzi, 1954). Bariéty, Kohler and Barbo (1953) have shown that it increases the fatalities from acute barbiturate poisoning in animals. Terzain (1952) has attempted an explanation of this barbiturate-chlorpromazine synergism based on his electroencephalographic studies. While barbiturate narcosis is secondary to an arrest of the of the continuous bombardment of the reticular formation from the cortex (or interruption of the afferent cortical pathways), chlorpromazine sleep is a primary effect due to a direct depressant action on the reticular formation whose tone controls the state of wakefulness.

In unpublished observations by the author it was noted that the potentiating effect of the intramuscular injection of 2 mg./kg. chlorpromazine on thialbarbitone narcosis in the dog reached its maximum 1½–2 hours after injection and persisted for almost 24 hours. Similar results were obtained with thiopentone and thioquinalbarbitone in the rat.

Autonomic Nervous System.

This action of chlorpromazine has attracted much attention, both from pharmacologists and clinicians. It is impossible to discuss in detail each of the observations on this subject, and for this reason the most important of these have been listed in table II. This deals first with its anti-adrenaline action followed by its anti-acetylcholine action, animal experiments being given before clinical observations in man. The findings reveal that chlorpromazine has a marked anti-adrenaline action and a feebler anti-acetylcholine effect.

The depressant action of chlorpromazine on autonomic activity was referred to as "ganglioplégique" by Courvoisier and her colleagues. Subsequent investigations have shown that this action is in no way comparable with what is called "ganglion block" in this country. Wien (1954) has shown that chlorpromazine blocks the effects of preganglionic stimulation on the nictitating membrane of the cat, but this may be a peripheral or central action rather than a true ganglion blocking effect. Decourt, Brunaud and Brunaud (1953a) point out that this classical test for ganglion blocking drugs may give erroneous results with chlorpromazine, since adrenaline acts as the chemical mediator on the terminals of the effector cells and chlorpromazine has a marked adrenolytic action. In low concentrations (1 mg./kg.) they found that preganglionic stimulation produces no contraction of the nictitating membrane, but since post-ganglionic stimulation likewise produces no contraction, the effect is obviously independent of any ganglion blocking activity of chlorpromazine. Confirmation of this view was obtained from the effects of chlorpromazine on the salivary activity of the submaxillary gland following stimulation of the corda tympani. Complete suppression of secretion occurred after administration of hexamethonium, but only very slight diminution after very large doses of chlorpromazine.

Cardiovascular system.

The majority of the cardiovascular effects observed after administration of chlorpromazine are secondary to its effects on the autonomic nervous system. This applies particularly to the postural hypotension with compensatory tachycardia.

The main effects reported in the electrocardiographic studies are variations in heart rate (Laborit, Huguenard and Alluaume, 1952; Couthier, 1953; Dobkin, Gilbert and Lamoureux, 1954; Moyer Kent, Knight, Morris, Huggins and Handley, 1954) and slight changes in the T-wave (Déchêne, 1954; Dobkin et al., 1954; Moyer et al., 1954). In the unanaesthetized rabbit no changes in the electrocardiogram were found after normal doses of chlorpromazine, but with subtoxic doses repeated at ten minute intervals there was an increase in atrioventricular and interventricular conduction times (Courvoisier et al., 1953). Moyer and his colleagues also found interventricular block following large dose (10 mg./kg.) in the dog and have reported one case in which this occurred in man. This, however, may have been attributable to a low serum potassium following prolonged vomiting. One other case of heart block in man is reported by Dobkin et al. (1954), but in this also it is difficult to decide what part the chlorpromazine played in its production.

On the isolated heart muscle Finkelstein, Spencer, Hammen and Albert (1954) have found a reversible reduction of contractile force and decreased irritability. Melville (1954) has also observed this depressant action of chlorpromazine on the isolated heart, but found that in spite of this there was an increase in the coronary blood flow, which finding was previously made by Courvoisier et al. (1953).

As well as causing vasodilatation through its action on the autonomic nervous system, perfusion of the isolated rabbit's ear has demonstrated a direct vasodilating action of chlorpromazine on blood vessels. This is accompanied by oedema which may be very marked, and microscopic examination shows serous fluid escaping from the greatly dilated vessels and distending the connective tissue. This irritant effect of chlorpromazine decreases with dilution and does not seem to depend on the pH of the solution (Courvoisier et al., 1953).

In vivo studies of the effect of chlorpromazine on capillary permeability shows it to have no effect in the guineapig. Large doses (12.5–50 mg./kg.) decrease permeability in the rat and rabbit (Courvoisier et al., 1953).

Respiratory System.

In the rabbit anaesthetized with urethane Courvoisier et al. (1953) have found that 0.05–2 mg./kg. chlorpromazine stimulates respiration and causes an increase in minute volume of 20–40 per cent. Larger doses cause respiratory depression and apnoea of varying duration.

Clinical reports on the whole tend to substantiate this finding that therapeutic doses of chlorpromazine have a respiratory stimulant action (Laborit, 1951; Alluaume, 1952; Laborit, Huguenard and Alluaume, 1952; Huguenard, 1953a; Laborit and Huguenard, 1954; Reckless, 1954). Alluaume (1952) finds that its use leads to sufficient respiratory stimulation to make hyperventilation apnoea difficult. Reckless (1954) has observed what he terms the "nalorphine-like effect" of chlorpromazine reversing respiratory arrest due to pethidine or morphine.

In contrast to all the clinical observations is the only report of the actual measurement of respiratory rate and volume before and following chlorpro-

TABLE II

Summary of the actions of chlorpromazine on the autonomic nervous system

Subjects	Observations	Reference
Dogs	Diminishes, abolishes or reverses adrenaline hypertension according to the dose of chlorpromazine used. Diminishes response to l-noradrenaline in doses which reverse effect of adrenaline. Depresses vasopresser carotid sinus reflex.	Pocidalo, Cathala, Himbert and Tardieu (1952). Courvoisier et al. (1953).
Dogs	Blocks response to adrenaline and l-noradrenaline on the isolated heart.	Melville (1954).
Dogs	Prevents adrenaline-chloroform induced ventricular fibrillation.	Finkelstein, Spencer, Hammen and Albert (1954). Melville (1954).
Rabbits	Protects against adrenaline induced pulmonary oedema.	Bariéty et al. (1953).
Dogs	Produces hypotension with decreased peripheral resistance.	Moyer, Kent, Knight, Morris, Huggins and Handley (1954).
Various animals	Reduces effect of cervical sympathetic to the iris.	Chauchard and Chauchard (1952).
Mice and rabbits	Decreases toxicity of adrenaline and l-noradrenaline.	Courvoisier et al. (1953).
Rats	Antagonizes local vasoconstriction due to adrenaline.	Courvoisier et al. (1953).
Man	Decreases effect of adrenaline on blood pressure and pulse.	Couthier (1953).
Man	Produces postural hypotension.	Laborit, Huguenard, and Alluaume (1952). Couthier (1953). Dobkin et al. (1954). Anton-Stephens (1954). Kent et al. (1954). Winkleman (1954).
Man	Bilateral Horner's syndrome. Small doses block all sympathetic vasopressor reflexes. Large doses block all vagal reflexes.	Dobkin et al. (1954). Melville and McIntosh (1954).
Cats	Inhibits the McSwiney response to duodenal dilatation.	Gray (1954).
Dogs	Diminishes response of heart to vagal stimuli. Slight diminution of acetylcholine induced hypotension.	Courvoisier et al. (1953).
Dogs	Reduces effect of stimulation of cut end of vagus in neck.	Pocidalo et al. (1954).
Rabbits	Feeble anti-spasmolytic action on isolated intestine.	Courvoisier et al. (1953).
Dog	Diminishes formation of gastric juice.	Courvoisier et al. (1953).
Man	Decreases gastric secretions, but does not abolish their response to insulin.	Dobkin et al. (1954).
Man	Partial protection against pleuro-pericardial reflexes during thoracic surgery.	Déchêne (1954).

mazine in man (Dobkin, Gilbert and Lamoureux, 1954). Respiratory depression, affecting both tidal volume and minute volume, followed intravenous or intramuscular injection of a single dose of 0.3–2 mg./kg. in conscious and anaesthetized patients. The effect on the respiratory rate was variable and often irregular. Conscious subjects receiving higher doses complained of conscious respiratory effort.

Drying of the secretions has been noticed after prolonged administration of chlorpromazine (Broglie, Jörgensen and Voss, 1953; Anton-Stephens, 1954; Kent, Knight, Morris, Dizon and Moyer, 1954). For this reason it has been recommended that special attention be given to oral sepsis, and minor respiratory complications in patients who are receiving the drug for a long time (Broglie et al., 1953; Anton-Stephens, 1954). Although there are no reports of the effect of chlorpromazine on the lumen of the respiratory tree observations have been made of its beneficial effect in asthma (Broglie et al., 1953; Robinson and Zuck, 1954). In the successful cases chlorpromazine was combined with pethidine and promethazine and it is impossible to say which of these drugs played the main part in relaxing the bronchial musculature.

Hepatic and Renal Function.

Cases of jaundice after chlorpromazine have already been referred to in connection with its possible breakdown in the liver. However, it does not follow that chlorpromazine *per se* is a hepatotoxic agent. Studies of serum bilirubin levels, bromsulphalein excretion and the thymol turbidity flocculation test in one series of 25 subjects revealed no abnormalities (Moyer, Kent, Knight, Morris, Huggins and Handley, 1954) while in another series (Lehmann and Hanrahan, 1954) abnormalities in the cephalin cholesterol test for liver function were detected in half the patients.

Rich and Resnick (1926), Schmidt, Unruh and Chesky (1942) and Davison, Lewis, Tagnon and Adams (1946) have all drawn attention to the deleterious effects of falls in blood pressure, with resulting anoxia, on hepatic function, the blood pressure changes are considered to be the cause of liver impairment following spinal analgesia (Boyce and McFetridge, 1938; Morrison, 1943; Engstrand and Friberg, 1945). It is interesting to note that abnormalities in liver function were only detected after the prolonged use of chlorpromazine in psychiatry, and not in the series where its administration only lasted one week. Whether the more prolonged period of hypotension played any part in producing hepatic damage is a matter of conjecture.

Transient hyperglycaemia has been noticed following the administration of chlorpromazine. Courvoisier et al. (1953) have observed that hyperglycaemia due to adrenaline is not affected by the drug. It may well be that this is a direct toxic effect of chlorpromazine on the liver.

Studies of renal function following chlorpromazine have been reported by Moyer et al. (1954) both in animals and in man. In dogs the slight fall in blood pressure that occurs was not associated with any significant changes in glomerular filtration and while variations in renal blood flow were inconsistent, if anything there was a tendency towards an increase. No changes in electrolyte excretion were

detected. These findings also applied to man and there were no deleterious effects of any kind on renal function.

Action on Metabolism.

Decourt (1953a) has suggested that the fundamental action of chlorpromazine is a reversible inhibition of cellular activity —'narcobiotic action'. This is attributed to an inhibition of certain enzymes, especially the dehydrogenases, which are essential for vital activity of all living organisms (Decourt, Gastel and Grenat, 1953). Inhibition of the activity of many micro-organisms has been demonstrated, chlorpromazine being bacteriostatic in concentrations of 1 : 15,000 to 1 : 33,000. This activity is limited to aerobic organisms; anaerobes, spores and viruses being unaffected, while the action is more marked in younger cultures with their greater metabolic activity. In higher concentrations the effect of chlorpromazine is irreversible (Decourt, 1953b).

Many unsubstantiated reports have claimed that chlorpromazine produces a reduction in oxygen consumption in man. In most of the techniques for which this claim is made chlorpromazine is combined with pethidine and/or other phenothiazine derivatives and sometimes with a mild degree of hypothermia (Laborit, 1951; Bobbio, Goffrini and Bezzi, 1952; Forster, Forster, Maier and Blum, 1952; Huguenard, 1952, 1953c; Crawford, 1954; Robinson and Zuck, 1954). Courvoisier et al. (1953) have shown that a single dose of 10–20 mg. chlorpromazine causes a reduction of about 20 per cent in oxygen consumption of the rat. this effect lasting up to six hours after administration with the larger doses. When daily doses are given, at the end of 36 days this depressant effect on metabolism could not be detected. The reduction in oxygen consumption was not due to the hypothermic activity of chlorpromazine. This effect on oxygen consumption could be due to the decreased activity of the animal brought about by the central depressant effect of the drug.

In vitro studies by Courvoisier and her colleagues have shown that chlorpromazine causes a decrease of oxygen consumption by cerebral cells, the degree of depression being in proportion to the concentration of the drug. This finding has been verified by Peruzzo and Forni (1953), who in addition found that chlorpromazine had no effect on oxygen consumption of either the liver or kidney.

In contrast to the above findings Dobkin, Gilbert and Lamoureux (1954) were unable to demonstrate any reduction in oxygen consumption following 1–2 mg./kg. chlorpromazine in man. In the conscious subject there was in fact often a slight increase in metabolism. This could possibly be due to the fact that some of the subjects were having simultaneous electrocardiographic, electroencephalographic, dynamometer and blood examinations.

Hypothermic Action.

Chlorpromazine has proved a valuable drug in facilitating the production of hypothermia by surface cooling, both in man and in animals (Courvoisier et al. 1953; Dundee, Gray, Mesham and Scott, 1953; Dundee, Scott, and Mesham, 1953; Dundee, Francis and Sedzimir, 1954; Friebel, Flick and Reichle. 1954; Ripstein, Freidgood and Solomon, 1954. It is more

effective than promethazine, pethidine or amidopyrine in this respect. Scurr (1954) reports a case in which, following 100 mg. chlorpromazine, the body temperature fell to 29°C during operation without any active cooling and Ratschow (1954) has observed a drop in body temperature in patients who were receiving the drug for psychiatric disorders.

The hypothermic action of chlorpromazine has been ascribed to its vasodilating properties, its effect on limbs being similar to that produced by paravertebral sympathetic block (Dobkin, Gilbert and Lamoureux, 1954). However, Dundee, Mesham and Scott (1954) have shown that chlorpromazine is more effective in facilitating the production of hypothermia than vasodilating drugs such as hexamethonium bromide or Rogitine. This difference they attribute to its ability to suppress shivering. The degree of fall in body temperature in response to cold is the difference between the amount of heat lost to the environment and that formed in the body. The latter is increased by the fibrillary muscle movements which are manifest as shivering.

While a tendency to render homeothermic subjects poikilothermic may be the main explanation for the clinical effectiveness of chlorpromazine in aiding the production of hypothermia, this is not its only action. Decourt, Brunaud and Brunaud (1953b) have demonstrated that animals given chlorpromazine, even when placed in environmental temperatures greater than their body temperature, undergo a relative hypothermia. Although the number of experiments they reported was small their findings were consistent, irrespective of the animal studied. Courvoisier et al. (1953) found that in rabbits the hyperthermic response to the Ducroy vaccine was abolished, and sometimes reversed, by the parenteral injection of 5 mg./kg. chlorpromazine. This effect was more marked than that produced by amidopyrine, the antipyretic action of which is greatly enhanced by the addition of chlorpromazine (Friebel et al., 1954).

Decourt, Brunaud and Brunaud (1953b) suggest that the hypothermic action of chlorpromazine is due to its reversible inhibition of cellular metabolism (Decourt, 1953a; Decourt, Gastel and Grenat, 1953), which has already been discussed.

Anti-emetic Action.

There is an abundance of evidence, both experimental and clinical, which shows that chlorpromazine possesses remarkable anti-emetic properties. It is particularly effective against that induced by drugs whose site of action is the chemoreceptor trigger zone in the floor of the fourth ventricle (Wang and Borison, 1952). These include apomorphine (Boyd, Cassell and Boyd, 1953; Courvoisier et al., 1953; Brand, Harris, Borison and Goodman, 1954; Cook and Toner, 1954; Glaviano and Wang, 1954; Isaacs and Macarthur, 1954), morphine and ergot (Brand et al., 1954; Glaviano and Wang, 1954). In therapeutic doses it is ineffective against that due to intravenous copper sulphate and lanatoside C, although part of the action of these is also thought to be on the chemoreceptor trigger zone. Veriloid emesis, due to action on the nodose ganglion of the vagus, is unaffected by therapeutic doses of chlorpromazine in animals and man (Brand et al., 1954; Isaacs and

Macarthur, 1954), although it is slightly decreased by large doses (10 mg./kg.) in animals.

While the anti-emetic action of small doses of chlorpromazine (up to 2 mg./kg.) seems to be due to its competitive blocking of the receptors at the emetic chemoreceptor trigger zone, Glaviano and Wang (1954) have postulated that in larger doses it has a direct depressant action on the vomiting centre. Their evidence is based on the finding that 4 mg./kg. effectively blocked vomiting due to oral copper sulphate in the dog.

Effect on Haemorrhagic and Traumatic Shock.

The work of Wiggers, Ingraham, Roemhild and Goldberg (1948) demonstrates that the so-called irreversible stage of shock is in part due to overaction of the compensatory circulatory mechanisms. The value of methonium compounds in preventing this overaction of the autonomic nervous system has been commented on in several recent publications (Du Cailar, 1953; Mondini and Fabris, 1953).

Given to a dog immediately after a severe haemorrhage, Courvoisier et al. (1953) found that intravenous injection of 2 mg./kg. chlorpromazine provided complete protection against "shock" which carried an 83 per cent mortality in non-treated animals. They found similar, though less striking results in the cat. Fournel (1952) who has also reported these findings concludes that it is the powerful adrenolytic properties of chlorpromazine which are responsible for its anti-shock activity. "By inhibiting the initial vascular phenomena caused by stimulation of the sympathetic system during haemorrhage or trauma, 4560 R.P. brings about reduced but sufficient oxygenation of the tissues, and protects the body from tissue anoxia which would otherwise have had fatal consequences."

A combination of chlorpromazine with hypothermia (28–30°C) has been studied for its effect on haemorrhagic shock in the chloralosed dog by Laborit, Jaulmes and Benitte (1952). Compared with controls the survival time is enormously prolonged and the classical picture of shock was absent. This work is the basis for the technique termed "artificial hibernation" by the continental workers. This will be referred to later in greater detail.

Anti-histamine Activity.

An early report on chlorpromazine stated that the drug is devoid of anti-histamine activity (Laborit, Huguenard and Alluaume, 1952). In the guineapig Courvoisier et al. (1953) have demonstrated protection lasting less than an hour against a histamine aerosol following subcutaneous injection of 20 mg./kg. chlorpromazine. Promethazine has more than 100 times this effect, 1 mg./kg. maintaining an antihistamine activity for 10 hours.

Toxicity.

The acute and chronic toxicity of chlorpromazine in animals has been reported by Courvoisier et al. (1953), and compared with that of other phenothiazine derivatives. As occurs with most other drugs there is a marked species variation in the $L.D._{50}$, the figures for the intravenous route being 50 mg./kg. for mice, 15 mg./kg. for rabbits, and 25 mg./kg. for rats, while that for oral administration in mice is 75 mg./kg. These are not

materially different from those reported for promethazine.

Following intravenous administration of large doses there is a sudden loss of muscle tone, which with lethal doses is followed by convulsions and death from respiratory arrest. In animals dying from acute poisoning hardly any evidence of hepatic damage was found. Small areas of congestion were found in the kidneys as compared with lesions of the convoluted tubules and glomerulitis from toxic doses of promethazine.

Large but sublethal doses produced a state of central depression with a considerable degree of hypothermia. The central depression lasted for more than four days and was of sufficient severity to prevent the animals from feeding. Promethazine in similar dosage produced depression which only lasted for 24 hours.

In the dog daily doses of 20 mg./kg. for one month resulted in no fatalities and apart from mild hyperglycaemia, no changes were detected in the blood. Smaller parenteral daily doses, 2 mg./kg., caused dilatation of the convoluted tubules and glomeruli at the end of one month, although, as with single lethal doses, this was less than occurred with promethazine. No kidney lesions were found after prolonged oral administration. The only other pathological lesion found after one month's medication with chlorpromazine was some thickening of lung tissue and areas of atelectasis, but this did not occur in every animal. Burn (1954) found that twice daily doses given to growing rats resulted in retardation of the growth. This may be attributable to its central depressant action particularly on the conditioned reflexes for food (Archer, 1954).

The toxic effects on the liver of prolonged administration to man have been referred to above. The hepatotoxic effect of the phenothiazine—the parent nucleus of chlorpromazine—have been known since 1941, and as pointed out by Hubble at that time (Hubble, 1941) this is not unexpected in view of its chemical structure. It is well know that substances containing benzene, such as trinitrotoluene, are poisonous both to the liver and blood elements. Although 2 cases of agranulocytosis following diethazine hydrochloride have been reported (Heller and Sime, 1952), Viaud (1954) believes that amine derivatives of phenothiazine have not a very marked action on blood.

No cases of agranulocytosis have been reported following intensive treatment with chlorpromazine but Anton-Stephens (1954) observed a leucopenia during the second week of parenteral treatment in 11 out of 23 patients in whom frequent blood examinations were carried out. This persisted until the drug was withdrawn or the dose reduced. In only one case did the leucopenia reach a figure below 3,000 per cu. mm. No changes were observed in subjects on oral therapy, and no changes in the red cells were observed in any of the patients. It has been suggested by Broglie, Jörgensen and Voss (1953) that changes in the erythrocytes may be responsible for elevation of the sedimentation rate which has been described by themselves and others (Anton-Stephens, 1954; Lehmann and Hanrahan, 1954).

A warning is issued by the manufacturers that dermatitis may result from the constant handling of chlorpromazine. Urticaria and other allergic manifesations have occurred in a few patients who were

receiving oral or parenteral chlorpromazine for psychiatric disorders (Lehmann and Hanrahan, 1954; Winkelman, 1954), but these cleared up when the drug was discontinued. Among the other toxic reactions to chlorpromazine, nausea, anorexia and epigastric distress have been reported, but the incidence of these is very low. It is not proposed to consider the soporific action or hypotensive effect of chlorpromazine under this heading, for while these may be undesirable side effects, they are part of the general pharmacological action of the drug.

Lemoine (1953) has reported a fatal accident at the end of anaesthesia which he attributes to premedication with chlorpromazine. He gives the cause of death as "syncope of respiration," but from the case report there would seem to be many other possibilities such as incomplete reversal of relaxant, pneumothorax, or even the combined hypotensive action of chlorpromazine, procaine amide, thiopentone and ether!

Miscellaneous effects.

Although neither competition nor depolarizing block of the myoneural junction is produced by chlorpromazine (Melville and McIntosh, 1954), the drug potentiates the effects of both types of muscle relaxants in animals and in man (Laborit, Huguenard and Alluaume, 1952; Courvoisier et al., 1953; Laba, 1953; Déchêne, 1954; Rizzi, 1954). Burn (1954) has shown that when chlorpromazine is administered to a cat it renders skeletal muscle unresponsive to direct stimulation. This paralysis is not sudden like the action of d-tubocurarine chloride but comes on slowly.

In common with other phenothiazine derivatives (Hutcheon, 1953) chlorpromazine possesses a local analgesic action, but if used in a concentration greater than 0.1 per cent may cause degeneration of the cytoplasm of the nerves. The systemic administration of chlorpromazine renders animals more susceptible to local analgesic drugs, both increasing their effectiveness and duration of action (Courvoisier et al., 1953).

Reilly and Tournier (1953) have found that chlorpromazine protected 55 per cent of mice from otherwise lethal doses of the endotoxin of typhoid fever. They point out that this is one of the first examples of a chemo-therapeutic agent being capable of suppressing the effects of a bacterial endotoxin.

CLINICAL USES

Anaesthesia.

The literature on the use of chlorpromazine before and during anaesthesia is very confusing, as most reports deal with it in combination with other drugs and it is sometimes combined with varying degrees of hypothermia. It is possible to divide the publications into three groups:

(*a*) Chlorpromazine alone given before anaesthesia in place of the routine premedication.

(*b*) Those where, although given before operation, its use is actually part of the anaesthetic technique. This includes the so-called "potentiated anaesthesia" and "artificial hibernation."

(*c*) The pre-operative administration of chlorpromazine to facilitate the production of hypothermia.

(*a*) The only report of the use of chlorpromazine alone is that of Dobkin, Gilbert and Lamoureux (1954). They found that the oral administration of 150 mg. on the night before operation, followed by 50 mg. by intramuscular injection one hour prior to scheduled surgery produced patients who were quieter and less apprehensive than those receiving morphine and atropine, pentobarbitone and atropine or atropine alone. Induction of anaesthesia was smooth and endotracheal intubation was facilitated. During operation a smaller quantity of anaesthetic agents was necessary to maintain anaesthesia. This applied to general, spinal and local agents. When the usual dose was administered anaesthesia was prolonged and because of this these workers considered it inadvisable to administer chlorpromazine after anaesthesia was induced. Although the patients looked poorly they did exceedingly well.

(*b*) Potentiated anaesthesia by phenothiazine derivatives was first described by Laborit in 1950, promethazine and diethazine being the drugs used. Goldblatt (1951) postulated that these drugs produced a partial block of the autonomic nervous system, thus diminishing the body's unfavourable reactions to surgical trauma. Chlorpromazine was later added to these drugs and its value in experimentally produced shock has already been discussed.

The technique practised on the Continent is extremely complicated, involving the use of a large number of drugs and sometimes mild hypothermia 'to potentiate the autonomic blockade'. Huguenard (1953c) has described it as "... a pharmacodynamic technique which, by using autonomicolytic drugs, aims at establishing a controlled inhibition of the autonomic nervous system, a neuroplegia of homeostasis, and as a consequence an attenuation of the regulatory reactions; it amounts to an economical method of living with a state of hypometabolism, muscular relaxation and twilight sleep which resembles narcosis"! Elsewhere he discusses the tendency in France to refer to artificial hibernation as "... à la fois l'état dans lequel se trouve un sujet soumis à une neuroplégie accompagnée de réfrigération, et la méthode qui permet d'obtenir cet état"; "neuroplégie" being defined as "... une déconnexion aussi complète que possible du système neuro-végétatif, et par voie de conséquence, du système endocrinien". He considers the proper description should be "..... un état physio-biologique stable" (Huguenard, 1953a).

For a full description of this technique and the many uses to which it has been put the reader is referred to Laborit and Huguenard's recent publication (1954) "Pratique de l'Hibernothérapie en chirurgie et en médicine". As pointed out by many workers there is no justification for the use of the term "artificial hibernation" to describe the technique (Kayser and Hiebel, 1952; Juvenelle, 1954). It is interesting to note that in a recent French publication chlorpromazine is omitted completely from the technique of "artificial hibernation" (Cahn, Dubrasquet, Bodiou and Melon, 1954).

In this country the aim seems to be "neuroplégie" as defined above. The techniques employed are much simpler

and consist of intramuscular or intravenous administration of chlorpromazine with promethazine, diethazine or pethidine before operation (Smith and Fairer, 1953; Baxter, Bolster and McKechnie, 1954; Beard, 1954). The advantages claimed include less apprehensive patients, less requirement for anaesthetic drugs (in some cases none at all is required), diminution of bleeding, absence of shock and decreased need for post-operative sedatives and analgesics. Sufficient clinical reports have not yet been published to allow a comparison of "autonomic stabilization" with orthodox means of anaesthesia.

(*c*) The pre-operative use of chlorpromazine to facilitate the production of hypothermia will be discussed later.

Production of Hypothermia.

The production of hypothermia by surface cooling is a simple matter in children because of their large surface area in relation to body weight, and possibly because of the poorly developed heat regulating mechanism. In adults chlorpromazine has proved of value in preventing peripheral vasoconstriction in response to the cold and thus preventing tissue temperature gradients. The drug is also capable of suppressing shivering, although this effect is somewhat erratic (Dundee, Mesham and Scott, 1954).

In the technique in vogue on the Continent pethidine, chlorpromazine and other pheno hiazine derivatives are administered until vasodilatation has occurred, and the patients are practically asleep. Ice bags are then applied or the patient placed on a cooling blanket (Laborit and Huguenard, 1952). Cooling by this method is sometimes difficult, with a slow fall in body temperature (Dundee, Gray, Mesham and Scott, 1953), the technique is cumbersome and time consuming and prolonged hypotension has followed its use (Preston and Wishart, 1954). Although some modifications have shortened the time required for the production of hypothermia (Reckless, 1954), the best results are obtained when chlorpromazine is given to the lightly anaesthetized patient (Dundee and Mesham, 1954; Ripstein et al., 1954). It may be that the potentiating of the anaesthetic and analgesic drugs by chlorpromazine makes the vasodilatation and suppression of shivering more complete.

When hypothermia has been induced with the aid of chlorpromazine it is often possible to obtain a valuable degree of postural ischaemia. Should it be desired to combine this technique with controlled hypotension, Arfonad or the methonium compounds can be used. However, much smaller dosage of these drugs will be required to produce the desired effect (Huguenard, 1953b; Dundee, Francis and Sedzimir, 1954; Hopkin, 1954).

A combination of the intrinsic hypothermic action of chlorpromazine and its ability to facilitate the production of hypothermia by surface cooling indicate its possible value in heat stroke and other hyperthermic states. Friebel et al. (1954) suggest its combination with amidopyrine for this, but one must question the wisdom of combining two drugs with potential granulocytopenic properties. Touraine (1953) has reported good results with chlorpromazine in five cases of severe head injuries in which hyperpyrexia was a presenting symptom.

Psychiatry.

The "pharmacological frontal lobotomy" effect of chlorpromazine has been used by many workers in the field of psychiatry. The drug has either been used alone (Tchekoff and Bouchard-Tournier, 1952; Molle and Nikorey, 1953; Sigwald and Bouttier, 1953; Anton-Stephens, 1954; Lehmann and Hanrahan, 1954; Winkelman, 1954) or in combination with other phenothiazine derivatives (Delay, Deniker and Tardieu, 1953; Deschamps and Cadoret, 1953; Ratschow, 1953). The method of treatment has varied with different workers, but the principle is to start with intramuscular doses of 25–50 mg./day, gradually increasing these until the desired effect is obtained, and at the same time substituting oral for parenteral therapy. The effective daily dose varies enormously and has been as high as 800 mg. Likewise the duration of treatment has varied from a few days to 8 months.

The drug has proved to be of value in the symptomatic control of most types of severe psychomotor excitement. Good results were also obtained in acute and chronic manic depressive patients in the maniacal phase (Lehmann and Hanrahan, 1954). Summarizing his results with 142 patients, Winkelman (1954) states "chlorpromazine . . . is a true therapeutic agent with definite indications, and is particularly outstanding in that it can reduce a severe anxiety, diminish phobias and obsessions, reverse or modify a paranoid psychosis, quieten maniac or extremely agitated patients and make hostile agitated senile patients quiet and easily manageable".

From the published reports on the use of chlorpromazine in psychiatry it would seem that the drug might have a place in the treatment of delirium tremens. It may also prove of value in controlling withdrawal symptoms in drug addicts.

Intractable Vomiting.

The anti-emetic properties of chlorpromazine have proved as remarkable in clinical practice as in the experimental animals. Its usefulness is not limited to vomiting due to drugs acting on the chemo-receptor trigger zone, and it seems to control emesis due to a large variety of causes. These include carcinomatosis, labyrinthitis, disulphiram and alcohol, uraemia, nitrogen mustard, digitalis, hyperemesis gravidarum, acute gastritis, and radiotherapy (Friend and Cummins, 1953; Howell, Harth and Dietrich, 1954; Kent, Knight, Morris, Dizon and Moyer, 1954; Kent, Morris, Rodgers and Knight, 1954). The inhibition of swing sickness observed in dogs (Cook and Toner, 1954) suggests that chlorpromazine might be of value in the prevention of motion sickness, but no reports of this use have been published.

Doses of chlorpromazine used to control vomiting have varied from 25 mg. daily to 50 mg. four times daily by intramuscular injection, and the duration of treatment has varied from 1 to 28 days. Most of the successful cases responded to one or two injections of 25–50 mg. chlorpromazine, and because of the small dosage the incidence of side effects was low. Kent, Knight, Morris, Dizon and Moyer (1954) have issued a warning that before the drug is used the cause of nausea and vomiting should be reasonably well established, otherwise a more serious condition may be obscured by the chlorpromazine.

Obstetrics and Gynaecology.

Chlorpromazine has been found of value in controlling hyperemesis gravidarum (Rouchy, 1952; Broglie, Jörgensen and Voss, 1953; Kent, Knight, Morris, Dizon and Moyer, 1954; Riding, 1954). Röttger (1953) has used it in combination with promethazine and pethidine for obstetrical analgesia. He obtained a satisfactory degree of sedation in over 80 per cent of the 150 patients treated. The analgesic effects were not so impressive—good relief was obtained in 38 per cent of cases, fair alleviation of pain in 37 per cent, and no beneficial effect in 25 per cent. No ill effects were observed on the baby although labour was slightly prolonged in primipara but of normal duration in multipara.

Schmidt-Elmendoroff (1953) has added chlorpromazine and other phenothiazine derivatives to Stroganoff therapy for eclampsia. He attributes the beneficial effects obtained to the smaller dosage of barbiturates and opiates which are required. The hypertension and hyperthermia of post-partum eclampsia were rapidly controlled by the use of chlorpromazine alone in a case reported by Rouchy and Creze (1953).

Intractable Pain.

The effect of chlorpromazine in potentiating analgesic drugs and its "pharmacological lobotomy" action have been put to use in the treatment of intractable pain. Sadove (1954) has found that 25 mg. chlorpromazine twice daily produced relief in 22 out of 28 cases who could no longer be made comfortable with large doses of narcotics and sedatives alone. The patients spoke of pain as an objective phenomenon which they no longer minded although it was still present. Howell, Harth and Dietrich (1954) found considerable benefit from its use in 18 out of 19 geriatric patients with severe pain. Their dosage of chlorpromazine varied from 50–75 mg. daily, and side effects were rare. These workers consider that chlorpromazine is worthy of an extended trial in geriatrics—not only for the relief of pain, but also for senile psychosis.

The author has studied the effect of daily oral doses of between 50–100 mg. chlorpromazine in over 60 cases of intractable pain, most of whom were not receiving great benefit from oral administration of routine analgesics. As far as was possible patients were not given parenteral injection of any drugs and most of them were treated in their homes with periodic visits to hospital. Among the early conclusions reached was the fact that chlorpromazine had no analgesic properties of its own. Adequate relief of pain was obtained in about three-quarters of the patients, and with very few exceptions they all received some benefit. The most satisfying combination of drugs proved to be chlorpromazine 25 mg. and l-methorphinan (Dromoran) 1.5 mg., three times daily.

Phaeochromocytoma.

The anti-adrenaline and hypotensive effects of chlorpromazine suggest that it might be of value in the diagnosis and anaesthetic management of cases of phaeochromocytoma. This hypothesis has been tested by the author in a 17-year-old girl whose spontaneous or Amechol induced hypertensive attacks were unaffected by benzodioxane, but could be reversed by intravenous injection of 5 mg. Rogitine

(Emlet, Grimson, Bell and Orgain, 1951; Gifford, Roth and Kvale, 1952).

Premedication with deep intramuscular injection of chlorpromazine 50 mg. and scopolamine 0.65 mg. did not prevent hypertensive attacks following thiopentone or positioning the patient on the operating table. The rise in blood pressure during these (180/110) was, however, much less than in her pre-operative attacks (240/135). Each of these attacks was cut short by 5 mg. Rogitine. Before handling of the tumour 15 mg. chlorpromazine was given intravenously and this completely suppressed any further hypertensive response. Its action lasted for at least 40 minutes as compared with 5–7 minutes for Rogitine. Neither drug had any effect on the tachycardia, the pulse rate reaching 200/minute during interference with the tumour. The fall in blood pressure at the end of operation was satisfactorily controlled by infusion of 1 : 250,000 l-noradrenaline.

Miscellaneous.

The inhibitory effect of chlorpromazine on gastric secretions and its spasmolytic action on the intestine have been put to use in the treatment of duodenal ulcers (Dobkin, Gilbert and Lamoureux, 1954). Symptomatic relief of symptoms was obtained, and relief was also obtained in the dumping syndrome.

These workers also obtained relief of pain in cases with severe vascular spasm, but no benefit was obtained in patients with complete vascular occlusion.

In most of the remaining clinical reports chlorpromazine is combined with other drugs and sometimes with hypothermia. Conditions treated include "neurotoxicosis" in children (Sorel, Bardier, Rieunau, Auban and Dalous, 1953); scarlet fever, bronchopneumonia, carbon monoxide poisoning (*Journal of the American Medical Association*, 1953); gunshot wounds (*Lancet*, 1954); and essential hypertension (Couthier, 1953).

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SOME ASPECTS OF HYPOTHERMIA AND AUTONOMIC BLOCK

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IN 1905 Simpson and Herring, from the Physiology Department in Edinburgh, published a revealing account of the effect on cats of severe cold—the cats were anaesthetized with ether and placed in a cold chamber at 4°C, where they remained for some hours (Simpson and Herring, 1905). Simpson wrote: "The temperature gradually falls, and when it has reached a sufficiently low point (about 25°C), the employment of an anaesthetic is no longer necessary; the animal at that temperature is insensible to pain and incapable of being aroused by any form of stimulation; it is in fact narcotized by cold and is in a state of what may be termed 'artificial hibernation'".

After a convincing description of the condition of these animals, nearly all of which recovered completely, Simpson and Herring concluded, "Cold narcosis compared with the anaesthesia produced by ether or chloroform is just as effective, but its application is tedious and not unattended with danger to life."

General hypothermia was neglected and its possibilities in clinical therapeutics went unrecognized until 1936, when Smith and Fay, observing a higher surface temperature in the breast than in the adjacent segments, and associating this with the high incidence of cancer, tried the effects of local hypothermia on cancerous growths. (Smith and Fay, 1939). They then combined local refrigeration with artificial hibernation for as long as five days, keeping the rectal temperature down to 30–32°C. Light narcosis was maintained with bromethol or the barbiturates and cooling achieved by complete exposure to temperatures of 10–15°C in an air-conditioned room,

Vaughn in 1940, adopting a similar technique in six malignant cases, demonstrated a definite reduction in metabolism but concluded that the procedure was hazardous and unjustified in the treatment of hopeless metastatic carcinoma. (Vaughn, 1940).

In 1950 Bigelow showed conclusively that, with progressive cooling of dogs anaesthetized with 2.5 per cent quinalbarbitone, rectal temperature and oxygen consumption bore an almost linear relationship (Bigelow et al., 1950). His records showed that at 10–12°C oxygen consumption would be nil or minimal, suggesting a state of suspended animation. He pointed out, however, that maintenance of life at this low temperature was not possible in the present state of our knowledge.

Bigelow stressed the fundamental importance of controlling shivering, and showed figures of doubled oxygen consumption with slight shivering, while

severe shivering could cause a threefold rise. He emphasized that no oxygen debt was incurred in the tissues even when cooling lasted for 14 hours, this being demonstrated by the complete recovery of the dog and by the absence of any notable rise in oxygen consumption on rewarming.

The regulation of body temperature depends on the posterior hypothalamus for the autonomic response to cold, but shivering is apparently controlled by a thalamic centre (*Brit. med. J.*, 1954). These centres control the complex response to cold which occurs on exposure of the surface of the warm-blooded animal. There is some recent evidence from the work of Delorme (1952) that cooling of the blood directly is a weaker stimulus to hypothalamic and thalamic responses.

Vasoconstriction is an early result of surface cooling, but may be inadequate in itself to maintain body temperature. Shivering will then occur and may increase oxygen consumption by 3 or 4 times. Further responses are the secretion of adrenal medullary and cortical hormones, while prolonged cooling may stimulate thyroxine secretion.

In all these physiological responses to cooling of the body surface is seen the difference between the poikilothermic and the warm-blooded animal. In effect, to ensure efficient cooling of the warm-blooded animal, it is necessary to cause a reversible change to the state existing in poikilotherms.

It has been suggested by Tait that the ability of cold-blooded animals to survive at temperatures of 2–3°C is due to the lower solidification temperature of their lipoids (Tait, 1922). Tait observed that the heart of the hibernating animal will still beat at 0°C. A frog may exist for months apparently without using any oxygen; certain bacteria and fish are known to survive at absolute zero (− 273°C). A link between hibernating animals and man is perhaps shown by the fact that premature and newborn babies may be poikilothermic for some hours or days; until puberty, temperature regulation is frequently unstable.

Other effects of cold exposure have been discussed by Talbott (Talbott, 1944, 1950) and Dill and Forbes (1941). They describe very intense arterial and venous constriction with loss of detectable arterial pulsation. The blood pressure is low but usually recordable; the pulse is slow. Thrombosis and arterial occlusion do not occur as a complication of general hypothermia but may, of course, result from freezing of an extremity. There is a slight shift to the left of the normal oxygen dissociation curve, and arterial oxygen tension shows a decline probably due to reduction in the rate of diffusion through the alveolar membrane, perhaps accentuated by slight fluid accumulation in the alveoli. Hyperventilation occurs, the carbon dioxide content of alveolar air may fall to 1.5 per cent or less, and there may be reduction of carbon dioxide combining power up to one-quarter. There may be haemoconcentration, leucocytosis, eosinopenia, and prolongation of coagulation time. Renal blood flow is greatly diminished with a reduction of up to 50 per cent in glomerular filtration rate. Cardiac arrhythmias have been reported by numerous authors when body temperature falls below 30°C. The lower the temperature the greater the likelihood

of dangerous arrhythmias, which prevent the safe use of hypothermic techniques below about 25°C.

In 1948 Dutta found that various drugs which antagonized acetylcholine could produce mild degrees of hypothermia. Pethidine, atropine, benadryl, procaine, and quinidine, all showed this effect. Dutta suggested that this was due to inhibition of acetylcholine in skeletal muscle, on which normal heat production depended. A greater fall in temperature was observed with these drugs after adrenalectomy (Dutta, 1948).

The action of a large number of antihistamines and anti-Parkinsonian drugs were studied extensively by the French pharmacologists, Courvoisier, Fournel and their colleagues (Courvoisier et al., 1953). While investigating the amine derivatives of phenthiazine they selected several drugs of potential importance to the anaesthetist. Foremost among these were promethazine, diethazine and, most recently, chlorpromazine.

The pharmacology of chlorpromazine in the laboratory animal has been described in detail by Courvoisier and her colleagues who elicited various complex central effects. Among these was an important potentiation of general anaesthetics such as hexobarbitone and ether, of hypnotics such as butobarbitone (Soneryl), of analgesics such as pethidine and morphine, of synthetic relaxants such as gallamine, and of local anaesthetics such as procaine. It was shown that chlorpromazine could produce effective hypothermia in mice, the temperature falling as low as 32°C. In dogs, however, the fall was not more than 2°C. Estimations of oxygen consumption in rats following a single dose of the drug were inconclusive and were not co-related with any fall in temperature, but it was demonstrated that chlorpromazine could to a large extent prevent the responses of the rat exposed to a temperature of 4°C. A comparison was drawn between this blocking effect on temperature regulation and the very similar effects seen in adrenalectomized animals. Courvoisier suggested that chlorpromazine transforms the homeothermic into the poikilothermic animal. Finally, chlorpromazine showed a very potent anti-emetic effect.

Some of these central effects had been demonstrated in several of the antihistamine group of drugs, but chlorpromazine, in spite of a close chemical relationship to these drugs, is almost without antihistamine action.

Courvoisier and her colleagues attribute to chlorpromazine a depressant action on the effects of vagal stimulation, but the evidence given seems inconclusive. More definite, however, is the action of the drug in antagonizing adrenaline and noradrenaline, and it is in this respect more effective than dibenamine. There is little evidence that chlorpromazine can produce blockade of autonomic ganglia. On the other hand, the drug seems as effective as dibenamine in protecting the dog from shock produced by artificial bleeding.

Bigelow et al. (1950) established in dogs that adequately deep general anaesthesia with barbiturates was a satisfactory means of preventing the hypothalmic stress responses to cooling of the body surface. The use of deep general anaesthesia, especially with non-volatile agents, may, however, be a disadvantage in the type of case where hypothermic techniques are indicated. The detoxication and excretion of

depressant drugs at low body temperature requires close investigation.

Curarization is effective in the prevention of shivering, but presumably does little to inhibit autonomic responses such as adrenaline secretion. A marked rise in metabolism, (Dill and Forbes, 1941) the result of hormonal stimulation, can occur without shivering.

On the evidence given by Courvoisier et al. (1953), Laborit and Huguenard constituted their "lytic cocktail" with the object of preventing reaction to all forms of stress including cold. (Laborit and Huguenard, 1951). Their intention was in fact to produce total autonomic inhibition. While Courvoisier and her colleagues did not produce convincing evidence of any peripheral ganglionic blockade by chlorpromazine, Laborit presumably believed that autonomic block occurred by direct action on the hypothalamic and thalamic centres.

Laborit affirmed that "the classical methods of defence are only to protect the constancy of the 'milieu interieur'—the essential basis of our freedom to withstand the external environment. This homeostasis is the result and the evidence of our evolution. But, if the constancy of our 'milieu interieur' is a guarantee of our freedom, it is not always a guarantee of our life. What we have occasion to say is that adaptation (after Selye) is a non-adaptation, but is a reaction to the demands of the 'milieu interieur'. The rôle of treatment is no longer to facilitate a proud struggle for the conservation of homeostasis. What we bring about with artificial hibernation is on the contrary a true controlled adaptation."

The efficiency of the "lytic cocktail" in facilitating hypothermia by surface cooling in dogs has been shown by Dundee and others. (Dundee et al., 1953a). General anaesthesia, curarization, and the "lytic cocktail" were found to be almost equally effective in preventing responses; it was clear, however, that of the drugs used in the "cocktail", chlorpromazine showed the greatest effect, both in promoting the fall in temperature and in preventing shivering. Pethidine inhibited shivering and allowed a slight fall in temperature; promethazine was almost without effect, and could well be omitted.

The technique used by Laborit and Huguenard was remarkable for its utilization of combinations of drugs with different pharmacological effects; they hoped to produce a true balanced adaptation by means of autonomic block and moderate surface cooling, combined with skilful use of drugs. They recommended procaine amide to achieve hypotension; cardiac cases were given spartine sulphate. In the post-operative period hypothermia might be continued up to 48 hours with administration of antibiotics, androgens, heparin, aneurine, and magnesium sulphate. At the stage of rewarming, thyroxine, vitamin C, prostigmine, and adrenaline were added, apparently as a stimulus to the cessation of artificial hibernation.

The state of artificial hibernation is described as follows: "The patient is unconscious with pink skin and mucous membranes; pulse is slow and full, about 80 per minute; the blood pressure is about 100/60; respiration is slow, deep, and regular; the pupils are small; analgesia is almost complete; body temperature is about 35.5°C." (Laborit and Huguenard, 1951). Ice is removed at that temperature,

but there is a further fall to 33–35°C, because of reduced heat production and blocking of temperature regulation.

The technique described by Dundee, Gray and others showed two important modifications from that of Laborit and Huguenard. (Dundee et al., 1953b). These workers eliminated many drugs employed by the French workers and also radically changed the emphasis in the procedure, their first object being to lower metabolism by surface cooling, the "lytic cocktail" assuring inhibition of cold stress responses. A serious disadvantage was the lack of control exerted on the level of body temperature. It is, moreover, difficult to understand the fall of 2–3°C on opening the chest; this might suggest that surface cooling produced extreme arteriolar constriction in the skin, driving the main blood volume into the deeper tissues and viscera, where the temperature would as a result be considerably higher than that at the body surface. The production of such temperature gradients may have deleterious effects on cardiac rhythm.

Difficulty was encountered in controlling shivering and producing effective hypothermia, and oxygen consumption did not fall consistently and in parallel with the fall in body temperature. A few isolated values of oxygen consumption taken during shivering revealed a rise in oxygen uptake of up to 20 per cent.

An important hazard pointed out by these workers is the derangement of clotting which may result from lowering of blood temperature. At 25°C the clotting time is prolonged to 3 or 4 times normal, but this is immediately corrected on rewarming. They found bleeding to be average or increased in almost half their patients and the amount bore little relation to the blood pressure level. Postural hypotension was frequent, however, following administration of the "lytic cocktail."

The operative procedures involved were major and the patients frail; nevertheless, while it must be admitted that on theoretical grounds a general lowering of metabolism could have benefited certain of these patients, analysis of the results achieved fails to reveal any positive practical advantage accruing from the use of hypothermia in this series. A more conservative approach to the surgery of the poor risk patient was made by Smith and Fairer, who reported a small series of cases involving major surgery. Their technique was a simplified version of that of Laborit and Huguenard, using the three drugs, chlorpromazine, pethidine and promethazine; cooling was not attempted. (Smith and Fairer, 1953).

In 1950, investigations into the effects of cold on the body tissues of dogs were started by Delorme (Delorme, 1952). His technique, a new approach, involved blood stream cooling by external arteriovenous fistula. Experience has shown that the optimal temperature for the successful application of Delorme's hypothermic technique is 25–27°C. At these temperatures, gross visceral ischaemia is not followed by signs of tissue damage. The temperature level is quite critical and an accidental rise in one instance to 30°C. during mesenteric arterial occlusion resulted in a fatal delayed infarction of bowel. At levels below 25°C, cardiac irregularities are increasingly common.

Blood stream cooling under light thiopentone or cyclopropane narcosis appears

to induce considerably fewer stress responses than surface cooling. Indications of stress response, such as eosinopenia, depletion of adreno-cortical lipids and ascorbic acid are not a feature. Shivering does occur, however, but responds easily to slight deepening of narcosis. There is a reduced arteriovenous oxygen difference in all tissues and organs except the heart, where there are indications of increased oxygen uptake. Cooling apparently reduces the oxygen demands of the tissues more than it reduces oxygen availability. When a vessel is ligated in an animal cooled to 25°C, blood at this temperature is no longer perfusing, and therefore no longer cooling the tissues supplied by the ligated vessel; yet the obviously extreme degree of anoxia which must result leaves the tissues undamaged, a fact which has been checked by histological examination. This phenomenon can only be explained on the basis of depression by cold of tissue enzymes. The supposition could be put forward that tissue enzyme systems are first depressed, then suspended, by cold; that they remain in this state although deprived of blood supply; and that they are reactivated either by the stimulus afforded by warm blood, or by a specific enzyme or group of enzymes present in the blood.

By the technique of Delorme, cooling can be accomplished at a rate of 0.5°C per minute, and control of body temperature level can be readily achieved.

Delorme has found that hexamethonium, when given to the cooled dog, does not affect the blood-pressure level; on rewarming, however, the drug may suddenly show its pharmacological effects. similarly, while adrenaline will increase the heart rate, it does not raise the blood-pressure. The peripheral effects of these drugs may be masked by the constriction produced by cold. Delorme has used acetylcholine to stop the heart under hypothermia, and asystole has been maintained for as long as 12 minutes. This action of acetylcholine can be abolished by atropine (Delorme, 1954).

Laborit suggested the use of chlorpromazine in addition to essential transfusion in the treatment of traumatic shock, while other workers have noted the extreme cardiovascular stability in patients treated by the technique of Laborit and Huguenard. Alluame goes further and has described these patients as being "unshockable" (Alluame, 1952). The protection from shock suggested by these workers and supported by the good results achieved by Smith and Fairer in their series, deserves further extensive investigation.

Blood flow is everywhere affected by sympathetic overactivity and while this is a compensatory mechanism in the maintenance of an adequate circulatory head of pressure, it may bring harmful sequelae if prolonged vasoconstriction is maintained. It has been shown that dibenamine can protect dogs from haemorrhagic shock produced by artificial bleeding (Josiah Macy Foundation, 1952). This action is apparently mediated by the ganglion-blocking and anti-adrenaline properties of dibenamine, which help to increase blood flow in the splanchnic vascular bed In dogs, death from shock can result from bacterial invasion of the peritoneal cavity and blood stream by organisms from within the intestinal lumen. Severe anoxia of the gut wall

allows this to occur and the action of dibenamine is thought to counter this anoxia with widespread splanchnic vasodilatation. The shock process may involve many different factors but the final mechanism is a disorder of blood flow leading to severe oxygen lack in the tissues.

Drugs which antagonize sympathetic activity may help to prevent shock from becoming irreversible provided that there is enough circulating blood to fill the dilated vessels. The danger of giving such a drug to the patient with diminished blood volume, in whom splanchnic vasoconstriction is the only factor maintaining an adequate blood flow to the brain and other organs, is obvious.

The production of vasodilatation by drugs in the shocked patient must be regarded with caution; this is especially true if there is a significant reduction of blood volume. Alluame describes a patient in severe shock to whom 50 mg. pethidine and 25 mg. chlorpromazine were given; although cyanosis disappeared and superficial veins became dilated, death occurred in a few minutes. This patient would appear to have needed transfusion to increase blood volume, with additional measures such as adoption of the Trendelenberg position, before centrally depressant drugs could safely be administered.

Wyman and Cox have described their use of pentamethonium and hexamethonium bromide in the production of hypotension and appear to be satisfied that ganglion-blocking agents can both prevent shock from developing and also prevent established shock from becoming irreversible (Wyman and Cox, 1953). This, however, requires more definite proof, both experimentally and clinically.

There is, therefore, a firm basis built largely from clinical impressions that autonomic blocking agents may be of benefit in the management of shock.

Sympathetic activity is increased by stimulation of the posterior hypothalamus, through which also reactions to cold are effected; this suggests that a centrally-acting drug like chlorpromazine, which has been shown to inhibit cold stress, will also depress sympathetic activity. There is inconclusive evidence that chlorpromazine is in fact a peripheral ganglion blocker, but sympathetic paralysis could be a result of its central effect. If this depressant action on the hypothalamus becomes fully confirmed in clinical practice, the drug could well be used as a substitute for morphine in cases where severe pain is absent, but where extreme vasoconstriction is increasing tissue anoxia and promoting a state of irreversibility.

At this early stage in the development of hypothermic techniques it is possible, although hazardous, to draw some preliminary conclusions from the experience gained by Laborit and Huguenard, by Dundee and Gray, by Smith and Fairer, and by Delorme.

Direct comparison of the technique of Laborit, on the one hand, and of Delorme on the other, should be avoided. Laborit's stated intention is to achieve a non-specific, diffuse autonomic block, and with this ensure complete stability of the central nervous and cardiovascular systems throughout major surgical procedures. There is little doubt that such a state of stability would be a desirable feature, but it is not conclusively estab-

lished that the two active constituents of the "lytic cocktail", chlorpromazine and pethidine, can in fact prevent neurogenic responses during severe surgical operations.

Conventional anaesthetic techniques have reached a stage where, instead of using one agent such as ether or cyclopropane which will produce widespread central nervous depression without discrimination, it is possible to use a combination of drugs each with specific action, for example:

Thiopentone and nitrous oxide for narcosis;
Pethidine for analgesia;
Curare for relaxation;
Hexamethonium or Arfonad for hypotension.

The question arises—can chlorpromazine be added to ensure stability of the autonomic nervous system?

In chlorpromazine there lies a strong challenge to the time-honoured use of morphine and the opium alkaloids in preoperative medication. Chlorpromazine induces mental calm; it antagonizes adrenaline; it is a powerful anti-emetic; it potentiates anaesthetics, analgesics, and hypnotics; it may also depress excessive autonomic discharge. The presence of all these properties in a single drug suggests for chlorpromazine a wide sphere of service where mental and physical tranquility are essential.

Early reports of surface cooling do not suggest that it is likely to compete seriously with direct blood-stream cooling where precision is required. Responses to surface cooling are marked, and require considerable suppression by drugs whose detoxication and excretion at low temperatures are obscure. Laborit aimed at a temperature level of 33–35°C, but it is doubtful whether oxygen consumption at this temperature would be reduced enough to affect the operative and post-operative course of his patients. The lower temperature level attained by Dundee and Gray did not provide any striking advantages, and it is difficult to avoid the impression that their cases could have been satisfactorily anaesthetized by more conventional methods.

On the other hand, if vasodilatation in the skin could be maintained, surface cooling might become more efficient in producing general hypothermia.

The future of direct blood stream cooling in neurosurgery and the surgery of the heart and great vessels appears unlimited. For critical operations of precision, where it is essential to deprive certain viscera of their blood supply, Delorme's technique has the advantages of being efficient, rapid, and readily controllable; in addition only light anaesthesia is required.

It is possible, however, to visualize a future for cooling in therapeutics, in the treatment of coronary thrombosis, for example, where rapid induction of hypothermia could tide the patient over until a collateral circulation is well established. Again, following internal carotid ligation, where hypothermia would preserve function until the normal side establishes control; even in obstetrical practice it is possible to visualize the applicaton of hypothermia; while the benefits of controlled hypothermia in the treatment of shock or any state of reduced oxygen availability, is obvious; finally, it may soon be possible to sustain very low levels

of hypotension over long periods by combining hypothermia with the use of vasodilating drugs; refrigerated blankets and mattresses may yet become essential features of the modern operating theatre. However, a technique involving the production of an external arteriovenous fistula seems unlikely to attain wide popularity outside specialized units. Improved methods of surface cooling may have a more promising future in general surgical units.

These techniques are revolutionary and formidable, but the words of Wilfred Trotter, quoted recently during the proceedings of the Anaesthetic Section of the Royal Society of Medicine, may not be out of place: "A little self-examination tells us pretty easily how deeply rooted is the fear of the new, and how simple it is when fear is afoot to block the path of the new idea by unbelief and call it scepticism, and by misunderstanding call it suspended judgment."

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ON "LOOKING UP THE LITERATURE"

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NOT the least important part of the preparation of a contribution to medical literature is the study of other published work on the subject to be discussed and the compilation of a bibliography or list of references to important articles. This task, unless it be undertaken in the right way, can be time-consuming and the cause of much irritation before final publication. If, however, the writer prepares his list of references fully and carefully as he goes along, he can submit his completed paper to the editor with confidence that there will be no need to check many of his references and fill in details that have been omitted. This task may prove difficult, particularly if journals have been borrowed from libraries in other centres. It is also essential that the writer should be familiar with the methods of obtaining information as to other papers with the least possible difficulty and delay, and that he should be able to submit his article for publication confident that he has not overlooked any important work already published in his subject.

MATERIALS AND METHOD FOR COMPILING REFERENCES

The mechanics of a satisfactory system of compiling a list of references are quite simple. The writer should obtain a quantity of ruled index cards, 8 in. by 5 in. is a convenient size, and preferably keep them in a suitable box-file, with a set of alphabetical guide cards if the list is likely to be a large one.

Details of the articles consulted are entered on the cards, the following information being written plainly; block capitals should be used, particularly for authors' names, as the time and effort so spent is well worth while to avoid difficulty at a later stage when confusion may arise and articles have to be sought for again. It is convenient to commence with the author's surname, followed by initials (in the case of papers by more than one author all their names should be entered in the order in which they appear in the journal), year of publication, title of journal or book, volume number, page at which the article commences and ends, title of paper. The remainder of the space on the cards may be usefully occupied by a synopsis of the article, or any details the writer may consider important.

The cards are filed alphabetically under authors' names, and so can be readily referred to as compilation of the paper proceeds. In some instances it may be preferred to keep the cards in chronological order, in which case the year of publication may be entered first, but as a general rule arrangement by authors' names will be found the most satisfactory method.

INDEXES TO GENERAL MEDICAL LITERATURE

The author must now trace relevant articles and it is an obvious, though not always appreciated, advantage to commence research with the most up-to-date indexes and work backwards. By this means the searcher will usually be rewarded, sooner or later, by discovering an article which gives a comprehensive survey of previously published work. When such an article is found the list of references appended to it will provide all the information required without further search.

There are two main sources of information regarding papers in medical periodicals, the *Quarterly Cumulative Index Medicus* and the *Current List of Medical Literature*. The latter has the advantage of being more up to date, since it appears monthly, but is not nearly so convenient to use as the *Index Medicus*.

The *Current List* is published by the U.S. Armed Forces Medical Library and indexes all periodical publications received in the library. It covers a wide field, and no important medical journal is omitted. The monthly issues contain contents lists of journals arranged in alphabetical order of titles with a subject index. Up to April 1954, an author index was also included, but for the future this will appear only in the half-yearly cumulative indexes. Every six months a cumulative subject and author index appears, and replaces the monthly indexes, covering the previous five months. The time-lag between the publication of articles and their appearance in the *Current List* varies according to the country of origin, but is not as a rule more than three or four months.

The *Index Medicus*, now published in half-yearly volumes, is compiled on the dictionary principle, subject and author entries appearing in one alphabetical sequence. The last volume published to date is that for the first half of 1952. It should also be borne in mind that the volume covering the first six months of 1949 has not yet appeared.

The subject headings employed in these two publications vary considerably, and in the *Current List* there are very few cross-references, so it is necessary to consider all possible headings before abandoning the search for an article on any particular subject. The headings also vary from volume to volume, and this is another source of difficulty for the unwary.

To explore the recent literature, the simplest plan is to use the *Current List* from the most recent issue back to the time covered by the latest volume of the *Index Medicus* and rely on the latter for earlier articles with the exception of the period already mentioned when the *Index Medicus* did not appear.

If the writer desires to include articles of historical interest in his list, then he would do well to make good use of the *Index-Catalogue of the Library of the Surgeon-General's Office*. The use of this catalogue is essential if a comprehensive review of the literature is contemplated. In its seventy-one volumes, published between 1880 and 1948, it covers a vast field from the earliest times to about 1945. Articles in the periodical literature are listed under subject only, books, theses, pamphlets, etc., under author and subject. The *Index* is published in four series, each series covering a complete alphabet with the exception of the fourth series, which ends

at Mez, and is the last volume which will be published. Users of this catalogue will find many changes in subject headings in the various series. Headings used in one may be abandoned in the next, with no cross-references or other indication of the change. It must also be remembered that in consequence of a temporary change of policy there is a gap in the subject entries covering the letters Ge–Z in respect of articles appearing between 1926 and 1932.

INDEXES TO LITERATURE ON ANAESTHESIA

The literature relating to anaesthesia, besides appearing in the comprehensive indexes mentioned above, is dealt with to greater or lesser extent in certain specialist publications. Each issue of *Anaesthesia* includes a list of articles on various subjects of interest to anaesthetists, presented under broad subject headings; *Current Researches in Anesthesia and Analgesia* contains an index, arranged by subject, of titles of articles on all branches of the speciality; and *Anesthesiology* includes a selection of abstracts of interesting articles.

ABSTRACTING JOURNALS

In many cases it is convenient to have access to abstracts of articles, to arrive at a decision whether it is necessary to consult the original paper, or to assess the quality of the subject matter of a contribution in a journal difficult to obtain.

Anesthesia Abstracts contains abstracts of varying length, arranged in alphabetical order of authors' names, with a subject index, of papers from a variety of journals. Reference may often profitably be made to *Abstracts of World Medicine*, *Excerpta Medica* (Surgery Section), *International Abstract of Surgery* and the *Journal of the American Medical Association*, as well as the specialist journals noted above.

Mention should be made here of a recent and useful publication under the title of *World Medical Periodicals*. This has been compiled under the auspices of a committee sponsored by WHO and UNESCO. It lists, in alphabetical order of titles, 3,908 periodical publications and indicates the abstracting journals, if any, which cover each item. A subject list is included, so that one may readily identify periodicals published throughout the world dealing with any specialty, and an index of countries of publication is also given.

THE LOCATION OF BOOKS AND JOURNALS

Having compiled a list of references, the writer's next task is to discover where they may be obtained. Books and journals not available in the libraries to which the inquirer has access may be obtained through the National Central Library. This is in effect a clearing house for obtaining publications on loan from a large number of co-operating libraries, known as " outlier libraries ", as well as providing material from its own stock. Many Continental university libraries lend through the National Central Library, so its scope is very wide.

It is usually more convenient, however, in so far as journals are concerned, to make use of the information given in the *World List of Scientific Periodicals*, which lists some 50,000 medical and scientific periodicals and gives their location in about 250 of the libraries of Britain. The entries are arranged in alphabetical order of titles,

with cross-references to changes of title, and the volume also gives an abbreviation of each title the form of which has become practically universally used as a standard by the majority of publishers. The *World List* includes only journals which existed between 1900 and 1950; for those which ceased publication before 1900 reference may be made to the *Union Catalogue of Periodical Publications in the University Libraries of the British Isles*. The *Union Catalogue* contains some 23,000 titles, but omits those in the *World List*, and the holdings of 113 University libraries are given.

Le Fanu's (1938) *British Periodicals of Medicine* is a further guide to the location of medical periodicals published in the British Commonwealth since 1684, in a few selected libraries.

LISTING OF REFERENCES

There is a diversity of methods of quoting references, but the one most generally adopted nowadays is that known as the "Harvard" system. It has many advantages over other systems, and is extremely simple in use. References in the *British Journal of Anaesthesia* are quoted according to this method, and therefore it need not be discussed in detail here.

THE GENERAL PREPARATION OF PAPERS FOR PUBLICATION

In conclusion it may not be inopportune to draw attention for the need for care in the general preparation of papers intended for publication in the medical press. Many excellent guides to this subject have been written, notably Sir Clifford Allbutt's *Notes on the Composition of Scientific Papers*, published in 1923, and a recent booklet by W. R. Bett which was reviewed in the March 1954 issue of the *British Journal of Anaesthesia*.

Attention to detail in the compilation of his list of references and in the presentation of his work will amply repay the would-be author, and avoid much wearisome checking and alterations to his paper when it reaches the proof stage.

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